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Pharmacokinetic interaction of intramammary ceftriaxone and oral polyherbal drug (Fibrosin®) in goats

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Abstract

Background: The aim of the present study was to determine pharmacokinetic interaction of ceftriaxone and polyherbal drug (Fibrosin®) in lactating goats following single dose intramammary administration of ceftriaxone with 1 h pre-single dose oral administration of Fibrosin®.

Methods: Pharmacokinetic interaction of ceftriaxone and Fibrosin® was evaluated in lactating goats following single dose intramammary administration of ceftriaxone at 50 mg/kg with 1 h pre-single dose oral administration of Fibrosin® (1.9 g). Estimation of ceftriaxone and its metabolite, ceftizoxime, was determined by high performance liquid chromatography.

Results: Fibrosin® treated goats showed a typical absorption-reabsorption phase of ceftriaxone in plasma following intramammary administration. Neither ceftriaxone nor ceftizoxime was detected in the plasma and urine of goats without Fibrosin® treatment, however, ceftriaxone persisted for 36 h and ceftizoxime was present from 48 h to 72 h in the plasma of Fibrosin® treated goats. Ceftizoxime was also available from 72 h to 360 h post-dosing in milk in the presence of Fibrosin® following intramammary administration of ceftriaxone suggesting the polyherbal drug played a major role in the penetration of ceftriaxone from milk to systemic circulation. Furthermore, the polyherbal drug increased the bioavailability of ceftizoxime in milk following the metabolism of ceftriaxone.

Conclusions: Polyherbal drug (Fibrosin®) plays a major role in the penetration of ceftriaxone from milk to systemic circulation and may be responsible for increased bioavailability of its metabolite in the mammary gland resulting in higher concentration and longer persistence of the drug in milk.

Keywords: ceftizoxime; ceftriaxone; goat; pharmacokinetics; polyherbal drug.

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Introduction

Ceftriaxone, a third generation cephalosporin, is being used more frequently for the treatment of lower respiratory tract infection, urinary tract infection, gonorrhoea, peritonitis, skin and soft tissue infections and septicemia caused by sensitive organisms. It is active against a wide range of gram negative and Gram positive organisms. The use of antibiotic therapy to treat and prevent udder infections in cows is a key component of mastitis control (1). Intramammary administration of antimicrobial agents is often practiced for the treatment of mastitis. Mastitis is a term which denotes an inflammatory condition of the mammary gland irrespective of causes. It is a global problem in livestock and causes huge economic loss. It is characterized by physical, chemical and microbiological changes in the milk and pathological changes in the glandular tissues of the udder. National Mastitis Council (NMC) estimated an overall loss to the dairy industry of $2 billion (approx. $180 per cow) due to mastitis (2). Selection of the antimicrobial agent and maintenance of adequate drug concentration at the site of infection are the most relevant problems in mastitis antibiotic therapy. Intramammary drug efficacy can be maximized by keeping the drug concentration at the site of infection above the minimum inhibitory concentration (MIC) as long as possible (3). Repeated administration of antimicrobial agent is often required to maintain MIC for an adequate period to cure mastitis which is not cost effective. Besides, the animals sometime suffer from systemic infection due to the spread of the microorganism from the infected mammary gland. But most of the antimicrobial agents cannot enter systemic circulation following intramammary administration due to poor penetration of the milk-blood barrier. The degree of drug passage from udder to bloodstream was investigated following intramammary administration of cefoperazone by measuring systemic drug absorption in healthy and mastitis-infected cows and it was observed that systemic drug absorption was negligible in healthy animals (0.020±0.006 μg/mL serum at 4 h), whereas it was higher in infected animals (3) (0.102±0.079 μg/mL at 4 h and 0.025 μg/mL) at 24 h. Cefotaxime and ceftazidime were administered separately to healthy and mastitic cows by intramammary route at 200 mg twice daily for three times and residues were present in the milk of both healthy and mastitic cows until 72 h post-dosing of either antibiotics. Both the drugs dispersed from the treated to untreated quarters when administered by the intramammary route (4); however, the degree of passage from the udder to systemic circulation was not determined in this study. Most of the lipophilic antibiotics tend to become trapped in the mammary gland and cannot reach systemic circulation at an adequate level following intramammary administration. Ceftriaxone, being a lipophilic antibiotic is not expected to

enter into systemic circulation following intramammary administration. It has been found that ceftizoxime, an active metabolite of ceftriaxone, persisted at a higher concentration for a longer period in milk of mastitic goats following single dose inravenous administration (5). Polyherbal drug Fibrosin® helps for cleansing of the udder tissue and let down of milk (leaflet on Fibrosin®) and is supposed to have bioenhancing properties and therefore may help the antibiotic to penetrate the milk-blood barrier. There is little literature related to effect of herbal drugs on pharmacokinetics of antimicrobial agents following intramammary administration particularly for ceftriaxone. Though the pharmacokinetic study of ceftriaxone was undertaken in many species following parenteral administration, e.g., cow calves (6), buffalo calves (7), lactating ewes (8) and lactating goats (5, 9), pharmacokinetic data following intramammary administration of ceftriaxone is unavailable. Hence, our present study was conducted to determine the plasma and milk level of ceftriaxone and/or ceftizoxime following single dose intramammary administration of ceftriaxone with 1 h pre-single dose oral administration of Fibrosin®.

Materials and methods

Drug

Ceftriaxone (analytical grade, purity ≥90%; Estral Pharmaceutical Industries, Vadadora, Gujarat, India) was used as test drug. Ceftizoxime (analytical grade, purity ≥90%) was obtained from Glaxo Smithkline Pharmaceuticals Ltd, Nashik, India. The components of Fibrosin (Legend Remedies Ltd, Vadadora, Gujarat, India), a polyherbal drug, are shown in Table 1.

Animal

A total of 12 clinically healthy lactating goats weighing between 8 kg and 12 kg body weight of approximately 1½–2 years of age were used in this experiment. The animals were caged individually in custom made metabolic cages (stainless steel) during experimental period. Artificial lighting facility was provided. Animals were stall-fed and the standard feed as well as water was provided *ad libitum*.

Design of experiment

The 12 goats were divided into two groups (Group I and II) consisting of six goats in each. For Group I: 50 mg/kg of ceftriaxone was administered to two teats of each goat after dissolving in 5 mL of distilled water and dividing it into equal portions. For Group II: 1 h before ceftriaxone was given at the same dose rate, a half bolus of Fibrosin® (1.9 g) was administered orally to each goat. The Institutional Animal Ethics Committee approved the experimental protocol before starting the experiment.

Collection of samples

Blood samples were collected at '0' (pre-dosing) and at 0.08, 0.16, 0.25, 0.33, 0.50, 0.66, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60 and 72 h post-dosing (pd) after which blood sample was not collected. Plasma was then separated and utilized for estimation of drug concentration. Urine samples were collected at 0, 24, 48, and 72 h pd for analysis of ceftriaxone/ceftizoxime. Milk samples were also collected at 0, 0.08, 0.16, 0.25, 0.33, 0.50, 0.66, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 240 and 360 h pd and utilized for estimation of the drug.

Analytical procedures

Extraction of ceftriaxone as well as its metabolite, ceftizoxime from plasma, milk and urine was done by modified method of Sar et al. (5).

Acetonitrile (1 mL) for ceftriaxone/mobile phase (1 mL) for ceftizoxime was added to a centrifuge tube containing 1 mL of plasma and was shaken vigorously for 1 min. The whole aliquot was centrifuged at 5000 rpm for 20 min. The supernatant was collected after passing through a filter paper (Whatman No. 1) and 20 µL of this was injected for HPLC assay.

Table 1 Components of Fibrosin®.

Kanchanar-gugal (*Bauhinia veriegata linn*)	Chitrak-mula (*Plumbago zeylanica*)	Punar-navastaka (*Triaanthema monogyna*)	Trifala (Myrobalan+Black Myrobalan+Emblic)-gugal (*Terminalia belerica Retz.+Terminalia chebula Retz.+Phylanthus amblica*)	Apamarga (*Achyranthes aspera linn.*)
Gummy materials, tannin, sterols	Flowers: Azulein (5-methoxy quercetin 3-rhamnoside), 3 rhamnosides of delphinidin	Alkaloid (punarnavine), other unidentified bases, fatty alcohol, sterols (β-sitosterol, α-sitosterol)	(a) Myrobalan fruit: Tannin, β-sitosterol, gallic acid, ellagic acid, ethyal gallate, galloyl glucose, chebulagic acid, mannitol, glucose, galactose, fructose, rhamnose (b) Black Myrobalan fruit: Tannin, polyphenolic compounds (chebulinic acid, chebulagic acid, gallic acid, corilagin, number of unidentified phenolic constituents), anthraquinone dye stuff (c) Emblic fruit: Vitamin viz., ascorbic acid, amino acid viz., glycine, tannin, polyphenolic compounds (viz., corilagin, ellagic acid, terchebin, gallic acid, chebulic acid, chebulagic acid, chebulinic acid), fixed oil, lipids viz., phosphatides, essential oil	Pungent oil, sterols viz., β-sitosterol and γ-sitosterol, terpenoid constituents

To a centrifuge tube containing 1 mL of milk/urine, acetonitrile (1 mL) for ceftriaxone/mobile phase (4 mL) for metabolite was added and shaken vigorously at 5000 rpm for 20 min. The supernatant was collected after passing through a filter paper (Whatman No. 1) and 20 µL of this was injected for HPLC assay.

A Hewlett-Packard (model 1050) liquid chromatograph coupled with a variable wave length UV-VIS detector and a 3392A integrator was used for the analysis of ceftriaxone and its metabolite, following the operational parameters; Mobile phase: Tetraheptyl ammonium bromide (3.2 g) dissolved in 400 mL of acetonitrile, 44 mL of buffered pH 7 and 4 mL of buffered pH 5 and made the volume 1000 mL with distilled water. The mobile phase, buffer pH 7 and buffer pH 5 were prepared as stated in USP. The whole mixture was filtered through a membrane filter of 0.5 µm and degassed by ultrasonification. Flow rate: 1.5 mL/min, Column RPC18 cartridge, λ: 280 nm.

Standard and samples (20 µL) were injected with Hamilton syringe (25 µL) into liquid chromatograph with the first and last being the standard. The recoveries of ceftriaxone and its metabolite (ceftizoxime) from plasma, milk and urine were estimated by adding known quantities of ceftriaxone and ceftizoxime to give final concentrations of 2, 5, 10 and 20 µg/mL. The area of HPLC peaks against several concentrations of ceftriaxone/ceftizoxime was plotted and linearity was found to be maintained. The linearity of the calibration curve was checked. The recovery of ceftriaxone was 80%–85% from plasma, 80%–82% from milk and 94% from urine, while for ceftizoxime the recovery was 82%–85% in plasma, 80%–85% in milk and 90%–92% in urine. The limit of detection for both ceftriaxone and ceftizoxime was 2 µg/mL and the sensitivity of the method for both ceftriaxone and ceftizoxime was 1 µg/mL. Stock solution of ceftriaxone and ceftizoxime (100 mg/L) and the mixture of both (50 mg/L, 50 mg/L) were prepared in HPLC grade water as external standards. The retention times of ceftriaxone and ceftizoxime were 2.40 and 1.11 min, respectively. The retention times of ceftriaxone and ceftizoxime occurring in plasma/milk/urine was compared with that of the external standard and the data were recorded in a HP 3392A integrator. Blank samples of plasma/milk/urine were also injected into HPLC before test samples and the chromatograms did not show any peak of ceftriaxone/ceftizoxime.

Pharmacokinetic analysis

Pharmacokinetic parameters of ceftriaxone in plasma were determined (10, 11). The same parameters of ceftriaxone and ceftizoxime in milk were determined from the computerized curve fitting program 'PHARMKIT' supplied by the Department of Pharmacology, JIPMER, Pondichery, India.

Pharmacokinetic parameters of ceftizoxime in milk in terms of the parent compound were calculated (12) using the effective ratio.

$$\text{Effective ratio} = \frac{\text{Molecular weight of metabolite}}{\text{Molecular weight of parent}}$$

$$\text{Concentration of parent} = \frac{\text{Concentration of metabolite}}{\text{Effective ratio}}$$

Statistical analysis

Drug concentration from different samples and pharmacokinetic parameters were determined for each animal individually and the mean value and standard error (SE) were calculated. Student's t-test was completed to find out the significance difference at 5% level (13). The data are presented in the text as the mean±SE.

Results

Plasma level

Mean values with SE of ceftriaxone concentration in plasma of lactating goats with Fibrosin® after single dose intramammary administration at 50 mg/kg have been presented in Figure 1. Neither ceftriaxone nor ceftizoxime could be detected in plasma of lactating goats in the absence of Fibrosin®. However, ceftriaxone was present in plasma at a concentration of 5.25±1.24 µg/mL at 0.08 h, achieved its maximum level of 57.50±6.06 µg/mL at 1 h and declined to a concentration of 3.00±0.31 µg/mL at 3 h in Fibrosin® treated goats. Furthermore, ceftriaxone concentration in plasma started to increase from 4 h (5.35±0.92 µg/mL), peaked at 8 h (52.75±7.36 µg/mL) and persisted until 36 h pd at a minimum concentration of 1.08±0.08 µg/mL in Fibrosin® treated lactating goats (Group II). Plasma concentration of ceftriaxone in goats treated with Fibrosin® showed two distinct absorption and reabsorption phases. Figure 2 shows that an adequate concentration of ceftizoxime was achieved (81.58±5.05 µg/mL) at 48 h, maintained a level of 98.85±8.45 µg/mL at 60 h and peaked at 72 h (120.00±11.54 µg/mL) in plasma of Fibrosin® treated goats following intramammary administration of ceftriaxone.

Pharmacokinetic parameters of ceftriaxone in plasma

Pharmacokinetics parameters of ceftriaxone following single dose intramammary administration with 1 h pre-single dose oral administration of Fibrosin® has been presented in Table 2. Mean values of K (distribution/elimination rate constant) and $t_{½}K$ (elimination half life) were, respectively, 1.47±0.003 h^{-1} and 0.47±0.001 h, while elimination rate constant (K') and elimination half life ($t_{½}K'$) values were 0.13±0.003 h^{-1} and 5.07±0.12 h. The mean values of absorption rate constant

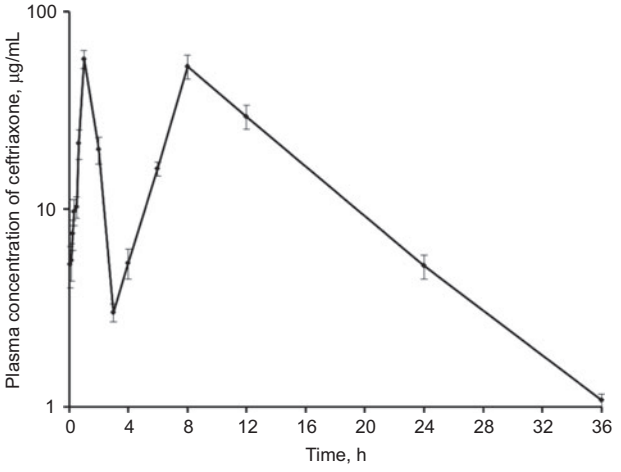

Figure 1 Semilogarithmic plot of mean plasma concentration of ceftriaxone (µg/mL) in lactating goats with 1 h pre-single dose oral administration of Fibrosin® (1.9 g) after single dose intramammary administration at 50 mg/kg.

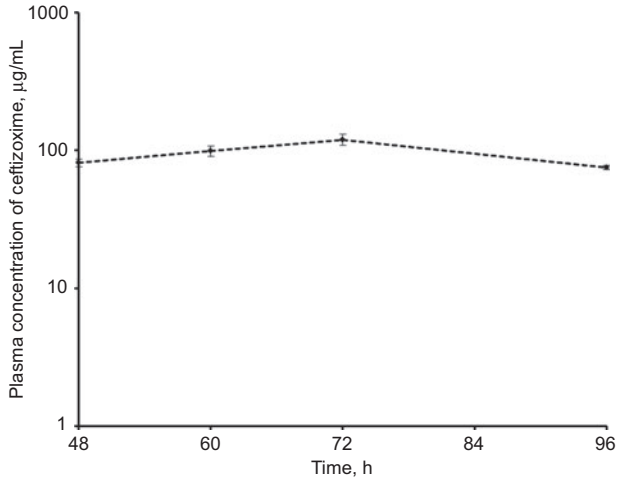

Figure 2 Semilogarithmic plot of mean plasma concentration of ceftizoxime (µg/mL) in lactating goats with 1 h pre-single dose oral administration of Fibrosin® (1.9 g) after single dose intramammary administration of ceftriaxone at 50 mg/kg.

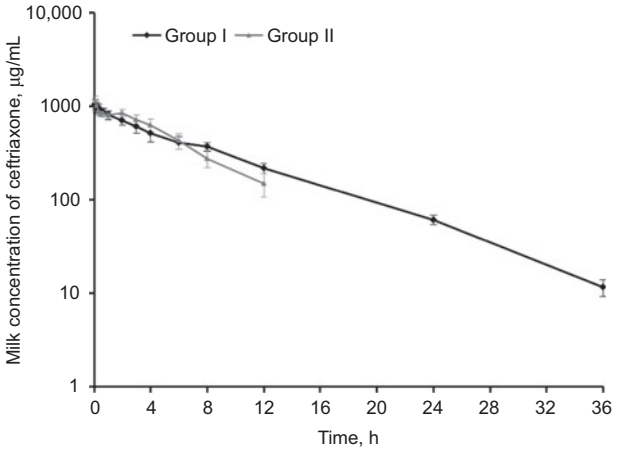

Figure 3 Semilogarithmic plot of mean milk concentration of ceftriaxone (µg/mL) in lactating goats without (Group I) and with (Group II) 1 h pre-single dose oral administration of Fibrosin® (1.9 g) after single dose intramammary administration at 50 mg/kg.

(*K*a) and absorption half life (t½*K*a) of absorption phase were 1.78±0.01 h^{-1} and 0.38±0.003 h, respectively, while reabsorption rate constant (*K*a′) and reabsorption half life (t½*K*a′) values were 0.24±0.01 h^{-1} and 2.89±0.14 h. Vd_{area} value was found to be 0.19±0.018 L/kg based on trapezoid method in the presence of Fibrosin® after single dose intramammary administration of ceftriaxone at 50 mg/kg.

Milk level

Mean values of milk concentration of ceftriaxone with and without Fibrosin® after single dose intramammary administration at 50 mg/kg have been displayed in Figure 3. Maximum milk concentration of ceftriaxone (1047.73±127.40 µg/mL) was achieved at 0.08 h in lactating goats without Fibrosin® administration. However, maximum and minimum mean milk concentrations of ceftriaxone were 1136.66±136.42 and 148.50±40.99 µg/mL at 0.08 h and 12 h, respectively, in Fibrosin® treated lactating goats. Either ceftriaxone or ceftizoxime could not be detected at 24 h and 36 h pd in milk of goats with Fibrosin® administration (Group II). Neither ceftriaxone, nor ceftizoxime could be detected in milk of lactating goats from 48 h pd onwards without oral administration of Fibrosin®. But ceftizoxime (380.16±46.18 µg/mL) was detected in milk from 72 h pd which gradually declined in concentration to 360 h with a concentration of 50.50±17.32 µg/mL in Fibrosin® treated goats (Figure 4).

Table 2 Mean kinetic parameters of ceftriaxone in plasma of lactating goats (Group I) with 1 h pre-single dose oral administration of Fibrosin® (1.9 g) after single dose intramammary administration at 50 mg/kg.

Kinetic parameters	Mean±SE
K, h^{-1}	1.47±0.003
t½*K*, h	0.47±0.001
*K*a, h^{-1}	1.78±0.01
t½*K*a, h	0.38±0.003
K′, h^{-1}	0.13±0.003
t½*K*′, h	5.07±0.12
*K*a′, h^{-1}	0.24±0.01
t½*K*a′, h	2.89±0.14
AUC, µgh/mL (based on trapizoid method)	1912.08±114.28
Vd_{area}, L/kg	0.19±0.018

AUC, total area under the plasma ceftriaxone concentration vs. time curve; *K*, distribution/elimination rate constant; *K*′: elimination rate constant; *K*a, absorption rate constant; *K*a′, re-absorption rate constant; t½*K*, distribution/elimination half-life; t½*K*a, absorption half-life; t½*K*′, elimination half-life; t½*K*a′, re-absorption half-life; Vd_{area}, apparent volume of distribution.

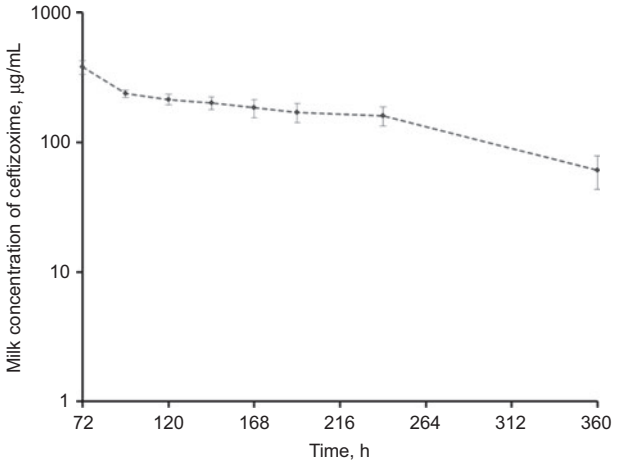

Figure 4 Semilogarithmic plot of mean milk concentration of ceftizoxime (µg/mL) in lactating goats (Group II) with 1 h pre-single dose oral administration of Fibrosin® (1.9 g) after single dose intramammary administration of ceftriaxone at 50 mg/kg.

Milk kinetics of ceftriaxone

The mean milk kinetic parameters of ceftriaxone have been incorporated in Table 3. The mean t½β value (5.77±0.15 h) was significantly increased ($p<0.05$) in lactating goats without the administration of Fibrosin® compared to the t½β value (4.14±0.54 h) in Fibrosin® treated group (Table 3).

Kinetic parameters of the metabolite in milk

Mean t½β and Cl_B values of ceftizoxime (metabolite) in milk of Fibrosin® treated lactating goats were found to be 87.00±13.80 h and 0.0009±0.0001 mL/kg/min; while Vd_{area} and AUC values were respectively, 0.006±0.0003 L/kg and 98292.07±17191.48 µgh/mL. The mean values of t½β and AUC suggest a longer persistence of ceftizoxime in milk.

Urine level

Mean urine concentration of ceftriaxone was 475.08±83.87 µg/mL at 24 h, while mean ceftizoxime concentration in urine were 81.75±20.46 and 75.00±11.54 µg/mL at 48 h and 72 h pd in Fibrosin® treated lactating goats. However, neither ceftriaxone nor ceftizoxime could be detected in urine samples of lactating goats without oral administration of Fibrosin®.

Discussion

Detectable concentration of neither ceftriaxone nor ceftizoxime was achieved in the plasma of lactating goats without Fibrosin® after single dose intramammary administration of ceftriaxone. Cagnardi et al. (3) reported a poor degree of drug passage from udder to systemic circulation in healthy cows following intramammary administration of cefoperazone (a third generation cephalosporin). Ceftriaxone, another member of third generation cephalosporin is a lipophilic drug (14) which may accumulate in lipid rich mammary gland tissue and does not cross the milk-blood barrier. In contrast, ceftriaxone was able to enter the systemic circulation and showed an absorption-reabsorption pattern in the plasma of lactating Fibrosin® treated goats and persisted to 36 h pd followed by the appearance of its metabolite, ceftizoxime, from 48 h onwards. Fibrosin® contains several components including chitrak-mula that have azulein (5-methoxy quercetin 3-rhamnoside) and quercetin which have bioavailability enhancing properties of different drugs (15–20). Hence, it is clear that Fibrosin® plays a major role in the penetration of ceftriaxone from the milk compartment to systemic circulation and acts as bioenhancer.

Hepatic clearance of ceftriaxone exceeds renal clearance (21). The non-renal elimination of ceftriaxone and cefoperazone is reported to be more rapid in sheep than in man (14). Hepatic clearance means the drug either undergoes metabolism or is excreted through bile. Appearance of ceftizoxime in the plasma of Fibrosin® treated goats and the maintenance of an adequate level for an appreciable period is due to the metabolism of ceftriaxone to ceftizoxime in the liver of goats (5). Furthermore, ceftriaxone, having a molecular weight of 554.59, is expected to excrete through biliary secretion. Arvidsson et al. (22) also reported 67% biliary excretion of ceftriaxone. Therefore, biphasic increased concentration of ceftriaxone after single dose intramammary administration in the presence of Fibrosin® may suggest enterohepatic circulation of ceftriaxone in goats. Stoeckel et al. (23) showed that ceftriaxone excreted in bile becomes microbiologically inactivated, and virtually no ceftriaxone is reabsorbed from the intestinal tract. Reabsorption of ceftriaxone from intestine may occur in goats which is responsible for the reabsorption cum elimination phase in the present study. The mean t½ value of ceftriaxone in milk of goats with Fibrosin® administration decreased drastically compared to goats without Fibrosin® administration which again strengthens the fact that Fibrosin® enhances the degree of passage of ceftriaxone from the mammary gland to blood.

Non-availability of ceftriaxone in the plasma of lactating goats without Fibrosin® after single dose intramammary administration of ceftriaxone is responsible for the absence of further appearances of ceftriaxone or ceftizoxime in milk after 36 h pd in these goats, but ceftizoxime was present at an adequate level from 48 h onwards in the plasma of Fibrosin® treated goats. Hence, ceftriaxone was excreted at a higher concentration in urine at 24 h pd in these goats followed by comparatively lower concentrations of ceftizoxime at 48 h and 72 h pd.

Therefore, it is concluded from the above study that Fibrosin® played a major role in the penetration of ceftriaxone from milk to systemic circulation and it may be responsible for increased bioavailability of its metabolite, i.e., ceftizoxime in mammary glands resulting in higher concentration and longer persistence of the drug in milk.

Table 3 Mean kinetic parameters of ceftriaxone in milk of lactating goats without (Group I) and with (Group II) 1 h pre-single dose oral administration of Fibrosin® (1.9 g) after single dose intramammary administration at 50 mg/kg.

Kinetic parameters	Group I	Group II
t½β, h	5.77±0.15	4.14±0.54[a]
Cl_B, mL/kg/min	0.009±0.0006	0.011±0.002
Vd_{area}, L/kg	0.0045±0.0005	0.0042±0.0006
AUC, µgh/mL	7838.51±915.05	5774.25±803.38

[a]$p<0.05$ compared to Group I.
AUC, total area under the plasma ceftriaxone concentration vs. time curve; Cl_B, the total body clearance of a drug representing the sum of all clearance process in the body; t½β, elimination half life; Vd_{area}, apparent volume of distribution (area method).

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
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References

1. Hillerton JE, Halley BI, Neaves P, Rose MD. Detection of antimicrobial substances in individual cow and quarter milk samples using Delvotest microbial. J Dairy Sci 1999;82:704–11.
2. National Mastitis Council. 2005 NE-1009, USDA Multistage Research Project, Questions and Comments. whurley@uiuc.edu.
3. Cagnardi P, Villa P, Gallo M, Locatelli C, Carli S, Moroni P, et al. Cefoperazone sodium preparation behavior after intramammary administration in healthy and infected cows. J Dairy Sci 2010;93:4105–10.
4. Rule R, Quiroga G, Buschiazzo H, Lacchini R, Mordujovich P. Rate of decline of cefotaxime and ceftazidime in milk following intramammary administration to healthy and mastitic dairy cows. Vet Rec 1998;143:310–1.
5. Sar TK, Mandal TK, Das SK, Chakraborty AK, Bhattacharyya A. Pharmacokinetics of ceftriaxone in healthy and mastitic goats with special reference to its interaction with polyherbal drug (Fibrosin®). Intern J Appl Res Vet Med 2006;4:142–54.
6. Soback W, Ziv G. Pharmacokinetics and bioavailability of ceftriaxone administered intravenous and intramuscularly to calves. Am J Vet Res 1988;49:535–8.
7. Dardi MS, Sharma SK, Srivastava AK. Pharmacokinetics and dosage regimen of ceftriaxone in *E. coli* lipopolysaccharide induced fever in buffalo calves. J Vet Sci 2005;6:147–50.
8. Goudah A, Shin HC, Shim JH, Abd Elaty AM. Characterization of the relationship between serum and milk residue disposition of ceftriaxone in lactating ewes. J Vet Pharmacol Ther 2006;29:307–12.
9. Ismail MM. Pharmacokinetics, urinary and mammary excretion of ceftriaxone in lactating goat. J Vet Med A 2005;52:354–8.
10. Pandey SN, Roy BK. Disposition kinetics of mebendazole in plasma, milk and ruminal fluid of goats. Small Ruminant Res 1998;27:111–7.
11. Baggot JD. Principles of drug disposition in domestic animals. In: the basis of veterinary clinical pharmacology. Philadelphia, London: W.B. Saunders Co., 1977.
12. Chanda D, Debnath S, Das S, Mandal TK, Bhattacharya A, Choudhury A, et al. Metabolism of metamitron in goat following a single oral administration of a nontoxic dose level: a continued study. J Agric Food Chem 2004;52:7377–81.
13. Snedecor GW, Cochran WG. Statistical methods. Iowa: Iowa State University Press, 1968.
14. Guerrini VH, Fillipich LJ, Cao GR, English PB, Bourne DW. Pharmacokinetics of cefaronide, ceftriaxone and cefoperazone in sheep. J Vet Pharmacol Ther 1983;8:120–7.
15. Choi JS, Han HK. The effect of quercetin on the pharmacokinetics of verapamil and its major metabolite, norverapamil, in rabbits. J Pharm Pharmacol 2004;56:1537–42.
16. Choi JS, Jo BW, Kim YC. Enhanced paclitaxel bioavailability after oral administration of paclitaxel or prodrug to rats pretreated with quercetin. Eur J Pharm Biopharm 2004;57:313–8.
17. Choi JS, Li X. Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. Int J Pharm 2005;13:1–8.
18. Lakhanpal P, Rai DK. Quercetin: a versatile flavonoid. Internet J Med Update 2007;2:22–37.
19. Randhawa GK, Kullar JS, Rajkumar. Bioenhancers from mother nature and their applicability in modern medicine. Int J App Basic Med Res 2011;1:5–10.
20. Shin SC, Choi JS, Li X. Enhanced bioavailability of tamoxifen after oral administration of tamoxifen with quercetin in rats. Int J Pharm 2006;313:144–9.
21. Sar TK, Mandal TK, Das SK, Chakraborty AK. Pharmacokinetics of ceftriaxone in carbon tetrachloride-induced hepatopathic and uranyl-nitrate induced nephropathic goats after single dose intravenous administration. Drug Metab Lett 2008;2:23–8.
22. Arvidsson A, Alvan G, Anvelin B, Borgi O, Nord CE. Ceftriaxone renal and biliary excretion and effect on colon microflora. J Antimicrob Chemother 1982;10:207–15.
23. Stoeckel K, McNamara PJ, Brandt R, Plozza-Nottebrock H, Ziegler WH. The effects of concentration-dependent plasma protein bindings on the pharmacokinetics of ceftriaxone (RO 13-9904), a new parenteral cyphalosporin. Clin Pharmacol Ther 1981;29:650–7.