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Comparative Pharmacokinetics and Milk Concentrations of Ceftazidime in Healthy and Mastitic Goats

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Abstract: Background: Mastitis is the single most common reason for antibiotics use in lactating dairy animals. Ceftazidime is a third generation cephalosporin belongs to the β-lactam antibiotics, has broad spectrum activity against pathogenic bacteria but there is no previous report concerning the use ceftazidime in mastitic goats. **The context and purpose:** The aim of the study is to establish disposition kinetics, absolute bioavailability and milk penetration of ceftazidime in healthy and mastitic goats following a single intravenous (IV) and intramuscular (IM) injections of 10 mg kg^{-1} b.wt. Serum and milk samples were collected at appropriate times during a 48 h administration interval and were analyzed by a microbiological assay method using *Escherichia coli* (ATCC 25922) as a reference organism. **Results:** Following single IV and IM injections ceftazidime concentrations were higher in mastitic than in healthy goats. The disposition of ceftazidime after a single IV injection was described by a two-compartment open model. The elimination half-life ($t_{0.5\beta}$) of ceftazidime was significantly faster in healthy (2.17 h) than in mastitic goats (2.68 h). The volume of distribution at steady state (V_{dss}) and total body clearance (Cl_{tot}) were significantly decreased in ($p \geq 0.01$) mastitic goats. Following IM administration, the peak serum concentration (C_{max}) was lower in healthy than in mastitic goats (6.58 and 9.50 μg mL^{-1}) and was achieved at a maximum time (t_{max}) 1.11 and 1.60 h., respectively. Serum protein-binding affinity of 9.05±0.63 and 12.62±1.09% was recorded in healthy and mastitic goats, respectively. Milk concentrations were higher in mastitic goats and the AUC_{milk}/AUC_{serum} and $C_{max\text{-}milk}/C_{max\text{-}serum}$ ratios indicated a wide penetration of ceftazidime from blood stream to mammary gland of mastitic goats. **Conclusions:** Ceftazidime could have been successful against susceptible mastitic pathogens in goats after parenteral administration.

Key words: Pharmacokinetics, ceftazidime, mastitis, milk, goats

INTRODUCTION

Mastitis is the most common and economically the most important disease of the dairy industry throughout the world (Neelesh, 2007; Halasa *et al*., 2007) especially in the peripartum period and costly problem for producers (Compton *et al*., 2009). The problem of mastitis is highly relevant not only for the economic losses to producers but also for the hygienic and safety production of dairy products intended for human consumption, particularly with respect to bacteriological quality. Intramammary infections in dairy goats are mainly of bacterial origin (Marin *et al*., 2007). Coliforms are probably among the major etiologic organisms of clinical mastitis in most dairies (Shpigel *et al*., 1997; Shathele, 2009). Among the gram-negative mastitis pathogens, *Escherichia coli* appear to be the most prevalent one. Ceftazidime is a third generation cephalosporin belongs to the beta-lactam group, a broad spectrum antibiotic, structurally and pharmacologically related to penicillins which work by inhibiting the bacterial cell wall synthesis (Judy *et al*., 2009). Ceftazidime is active against facultative or aerobic Gram-negative bacilli (*Escherichia coli, Proteus* sp., *Klebsiella* sp., *Enterobacter* sp., *Salmonella* sp.) (Salehi and Bonab, 2006). Ceftazidime is also active against some gram-positive pathogens (*Staphylococcus* sp., *Streptococcus* sp.) and is very active against *Pseudomonas aeruginosa* (Moore *et al*., 2000; Albarellos *et al*., 2008; Sisecioglu *et al*., 2011). Pathologic changes induced by *E. coli* endotoxin have modified the pharmacokinetic behavior of several drugs in different species (Tanira *et al*., 1997; Chaundhary *et al*., 1999). The use of antibiotics for mastitis treatment is one of the most important causes of violative antibiotic residues in milk and meat of treated animals. Pharmacokinetics of ceftazidime has been investigated in rabbits (Abd-El-Aty *et al*., 2001), cats (Albarellos *et al*., 2008), calves (Soback and Ziv, 1989), sheep (Rule *et al*., 1991)

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and cows (Rule *et al*., 1996). However, there have been no previous reports for ceftazidime pharmacokinetics in goats. Consequently, the aim of this study was to establish disposition kinetics, absolute bioavailability and milk penetration of ceftazidime in healthy and mastitic goats after single IV and IM administration at a dose rate of 10 mg kg^{-1}. Moreover, to estimate an appropriate dosage regimen of ceftazidime in goats, using the surrogate markers of pharmacokinetic-pharmacodynamic integration (C_{max}/MIC and AUC/MIC).

MATERIALS AND METHODS

Drug: Ceftazidime (Fortum, Glaxo Smith Kline S.A.E., El-Salam City, Cairo, Egypt) was reconstituted in sterile water (concentration of 10%) just prior to administration.

Animals: Twenty Balady female goats (ten healthy and ten naturally mastitic) selected from the field and from the animal farm, Faculty of Veterinary Medicine, Beni-Suef University were used. Mastitic goats suffer from increased rectal temperature (39.5±0.17°C), anorexia, depression and signs of udder inflammation (swelling, hotness and abnormal size) and abnormal milk. Mastitis confirmed by California Mastitis Test and by bacteriological examination of milk for isolation and identification of the causative organism (Sharma *et al*., 2007). Bacteriological examination revealed that the animals were infected with *Escherichia coli* pathogen. Animals were 3-5 years-old and weighing 25-33 kg b.wt. and were fed on hay, concentrated mixture and green fodder and fresh water *ad libitum*.

Experimental designL: Five goats in each group (healthy and mastitic) were given 10 mg kg^{-1} ceftazidime intravenously into the right jugular vein. The other five goats in each group were given the same dose of the drug intramuscularly into the deep gluteal muscle of hindquarter.

Blood samples from all 4 groups were collected via vein puncture from jugular vein before and 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24 and 48 h post-administration.

Milk samples were collected by hand stripping at 0.5, 1, 2, 4, 6, 8, 10, 12, 24 and 48 h post-administration after complete evacuationof the udder to avoid a dilution effect. Blood samples were left to clot at room temperature then centrifuged at 3000 revolution per minute for 10 min. to obtain clear serum. All samples were kept frozen at -20°C until analyzed. All samples were assayed in the same week after collection. Bacteriological examination was performed for udder pathogens for isolation of the pathogenic causative bacteria. The Minimum Inhibitory Concentration (MIC) of ceftazidime for isolated causative agent was determined using a micro-titration broth dilution technique (Spreng *et al*., 1995).

Ceftazidime bioassay: Serum and milk concentrations of ceftazidime were determined by microbiological assay according to the method of Tsai and Kondo (2001) using *Escherichia coli* (ATCC 25922) as a reference organism (Albarellos *et al*., 2008). The tested micro-organism was included in Mueller-Hinton agar medium (Oxoid LTD., Basingstoke, Hampshire, England) and equidistant wells were cut into the agar. Standard concentrations of ceftazidime were prepared in antibiotic free goat's serum and milk and in phosphate buffer saline (pH 7.0). The standard curves for serum, milk and buffer were linear between 0.156 and 10 μg mL^{-1} ceftazidime with a typical correlation coefficient >0.98-0.99 for serum, milk and buffer. The minimal quantification level for the assay method was 0.156 μg mL^{-1}. The serum protein-binding of the drug was determined *in vitro* according to the method of Craig and Suh (1980) which is based on the diffusion of the free antibiotic into the agar medium. To estimate the protein binding of ceftazidime, the drug was dissolved in antibiotic free goat's serum and milk and in phosphate buffer saline (pH 7.0) at concentrations of 0.156, 0.3125, 0.625, 1.25, 2.5, 5,10 and 25 μg mL^{-1}. The differences in the diameter of the inhibition zone between the solutions of the drug in the serum, milk and buffer were calculated. The percentage of protein-bound fraction was calculated by the following equation:

$$\text{Protein binding (\%)} = \frac{\text{Zone of inhibition in buffer-Zone of inhibition in serumi}}{\text{Zone of inhibition in buffer}} \times 100$$

Pharmacokinetic analysis: Serum concentrations of ceftazidime for each individual goat were subjected to a compartmental analysis using a nonlinear least-squares regression analysis with the help of a computerized curve-stripping program (R Strip; Micromath Scientific Software, Salt Lake City, UT, USA) (Abo-EL-Sooud and Goudah, 2010). For IV and IM, the appropriate pharmacokinetic model was determined by visual examination of individual concentration-time curves and by application of Akaike's Information Criterion (AIC) (Yamaoka *et al*., 1978). After IM administration, data was analyzed by adopting a one-compartment open model. This program also calculated non-compartmental parameters using the statistical moment theory (Gibaldi and Perrier, 1982). The C_{max} (maximum serum concentration) and t_{max} (time of maximum serum concentration) were taken directly from the curve. The terminal elimination half-life ($t_{0.5el}$) and absorption half-life ($t_{0.5ab}$) were calculated as $\ln 2/K_{el}$ or $\ln 2/K_{ab}$,

respectively, where K_{el} and K_{ab} are the elimination and absorption rate constants, respectively. The area under serum concentration-time curve (AUC) was calculated by the method of trapezoids. The Mean Residence Time (MRT) and mean absorption time (MAT) were calculated as MRT = AUMC/AUC and MAT = $MRT_{i.m}$-$MRT_{i.v}$. The total body clearance (Cl_{tot}) was calculated as Cl_{tot} = Dose/AUC and the absolute bioavailability (F) as $F = AUC_{i.m}/AUC_{i.v} \times 100$. The extent of drug penetration from the blood into the milk was expressed as the ratios of AUC_{milk}/AUC_{serum} and $C_{max\text{-}milk}/C_{max\text{-}plasma}$ (Marin *et al*., 2007).

Pharmacodynamic analysis: Pharmacodynamic efficacy of ceftazidime was determined by calculating the C_{max}/MIC and AUC/MIC ratios following IM administration using MIC of *E. coli* isolated from naturally mastitic goats. These ratios represent the inhibitory activity or surrogate markers of efficacy of ceftazidime against *E. coli* (Mckellar *et al*., 2004).

Statistical analysis: The statistical analysis was performed using the SPSS®10.0 software package (SAS, Cary, NC, USA). Results are presented as arithmetic Mean±SE. The nonparametric Wilcoxon test was used to compare the parameters collected in healthy and mastitic goats following each route of administration. Means were considered significantly different at $p<0.05$ and $p<0.01$.

RESULTS

Following IV administration of ceftazidime (10 mg kg^{-1}) in healthy and mastitic goats, the serum concentrations versus time data follow the two compartment open model and exhibit a biphasic decline (Fig. 1). The pharmacokinetic parameters of ceftazidime following IV administration in healthy and mastitic goats are shown in Table 1. Concentrations of ceftazidime in serum and milk after IV and IM injections exceeded the MIC of the tested micro-organism. The elimination half-life ($t_{0.5\beta}$) of ceftazidime was significantly faster in healthy (2.17 h) than in mastitic goats (2.68 h). As compared with healthy goats, the values AUC and MRT were significantly higher, whereas Vd_{ss} and Cl_{tot} were significantly lower following IV administration of ceftazidime in mastitic goats.

Ceftazidime was absorbed and eliminated rapidly after IM administration in healthy goats. The C_{max} were 6.58 and 9.50 μg mL^{-1} and attained at t_{max} of 1.11 and 1.60 h in healthy and mastitic goats, respectively (Fig. 2.). The pharmacokinetic parameters of ceftazidime following IM administration in healthy and mastitic goats are shown in Table 2. The systemic bioavailabilities of IM dose were

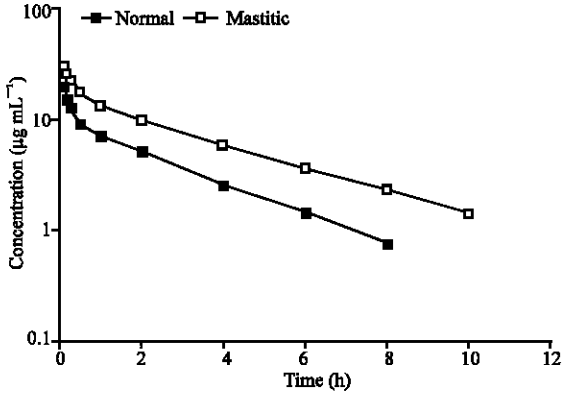

Fig. 1: Semi-logarithmic graph of the mean (±SE) serum ceftazidime concentration-time profile after a single IV administration of 10 mg kg^{-1} b.wt. in healthy goats

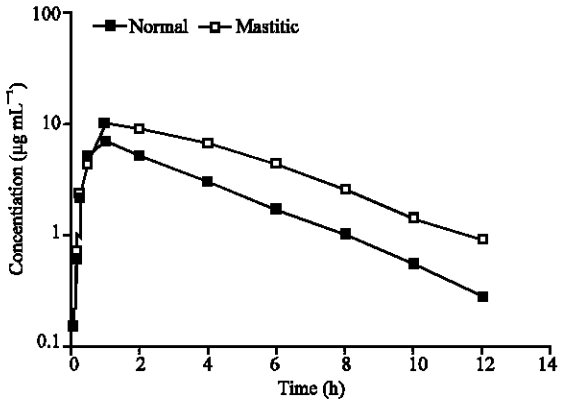

Fig. 2: Semi-logarithmic graph of the mean (±SE) serum ceftazidime concentration-time profile after a single IM administration of 10 mg kg^{-1} b.wt. in mastitic goats

83.94 and 81.43%, respectively. Serum protein-binding capacity of 9.05±0.63 and 12.62±1.09% was recorded in healthy and mastitic goats, respectively. The MIC of the drug was 0.25 μg mL^{-1} for *E. coli* isolated from the mastitic goats. The C_{max}/MIC and AUC/ MIC ratios were significantly higher in mastitic goats (38 and 230 h) than in healthy goats (26 and 114 h). The obtained results for surrogate markers of antimicrobial activity of ceftazidime (C_{max}/MIC and AUC/MIC) in mastitic goats with *E. coli* can be expected to optimize the clinical efficacy and minimize the development of resistance.

Milk concentrations of ceftazidime after IV and IM injections in healthy and mastitic goats are shown in Table 3. The concentrations were higher in mastitic goats and the drug was detected in milk up to 12 and 24 h in healthy and mastitic goats, respectively. The

Table 1: Serum and milk pharmacokinetic parameters of ceftazidime (Mean±SE) in healthy and mastitic goats following a single IV administration at a dose rate of 10 mg kg^{-1} b.wt. (n = 5)

Parameter	Unit	Healthy goats	Mastitic goats
Serum			
α	h^{-1}	6.60±0.35	4.29±0.10**
β	h^{-1}	0.32±0.01	0.26±0.015*
K_{12}	h^{-1}	3.50±0.09	1.85±0.06
K_{21}	h^{-1}	2.61±0.09	2.19±0.11
K_{el}	h^{-1}	0.81±0.06	0.51±0.088
$t_{0.5\alpha}$	h	0.11±0.005	0.16±0.007**
$t_{0.5\beta}$	h	2.16±0.12	2.68±0.11*
MRT	h	2.84±0.07	3.57±0.11**
AUC	µg.h mL^{-1}	34.04±2.48	70.56±5.33**
V_c	L kg^{-1}	0.40±0.03	0.28±0.02*
Vd_{ss}	L kg^{-1}	0.83±0.04	0.51±0.03**
Cl_{tot}	L/kg/h	0.29±0.03	0.14±0.01**
Milk			
C_{max}	µg mL^{-1}	0.82±0.06	2.02±0.05**
t_{max}	h	2.10±0.04	2.62±0.07
$t_{0.5el}$	h	2.32±0.18	2.08±0.17
AUC_{milk}	µg.h mL^{-1}	5.46±0.11	13.42±0.87
AUC_{milk}/AUC_{serum}	Ratio	9.50±0.19	19.02±1.32**

*p<0.05 **p<0.01. α, β hybrid rate constants representing the slopes of distribution and elimination phases, respectively; k_{21}: First-order constant for transfer from peripheral to central compartment; K_{el}: Elimination rate constant; k_{12}: First-order constant for transfer from central to peripheral compartment; $t_{0.5\alpha}$: Distribution half-life; $t_{0.5\beta}$: L elimination half-life; MRT: Mean residence time; AUC: Area under serum concentration-time curve; V_c: Apparent volume of the central compartment; Vd_{ss}: Volume of distribution at steady state; Cl_{tot}: Total body clearance. C_{max}: Maximum milk concentration; t_{max}: Time to peak milk concentration; $t_{0.5(el)}$: Elimination half-life; AUC_{milk}: Area under the milk concentration-time curve from zero to infinity; AUC_{milk}/AUC_{serum}: The ratio of penetration of the drug from the blood into milk; $C_{max\text{-}milk}/C_{max\text{-}serum}$: The ratio of penetration of the drug from the blood into milk

Table 2: Serum and milk pharmacokinetic parameters of ceftazidime (Mean±SE) in healthy and mastitic goats following a single IM administration at a dose rate of 10 mg kg^{-1} b.wt. (n = 5)

Parameter	Unit	Healthy goats	Mastitic goats
Serum			
kab	h^{-1}	2.22±0.11	1.49±0.10
Kel	h^{-1}	0.33±0.07	0.23±0.03
t0.5ab	h	0.31±0.03	0.47±0.03*
t0.5el	h	2.11±0.11	3.05±0.13**
Cmax	µg mL^{-1}	6.58±0.40	9.50±0.73*
tmax	h	1.11±0.08	1.60±0.09*
AUC	µg.h mL^{-1}	28.57±1.95	57.46±4.37**
MRT	h	3.41±0.21	5.19±0.39*
MAT	h	0.57±0.01	1.62±0.087**
F	%	83.94±6.00	81.43±6.51
IBD	h	11.71±0.75	18.52±1.00
Milk			
Cmax	µg mL^{-1}	0.60±0.07	1.93±0.09**
tmax	h	2.25±0.10	2.53±0.06
t0.5el	h	4.01±0.22	3.00±0.39
AUCmilk	µg mL^{-1}	5.06±0.33	13.74±1.20
AUCmilk/AUCserum	Ratio	17.72±1.32	23.91±1.75*
Cmax-milk/Cmax-serum	Ratio	9.12±0.51	20.36±1.62 **

*p<0.05, **p<0.01. k_{21}: First-order absorption rate constant; K_{el}: First-order elimination rate constant; C_{max}: Maximum serum concentration; t_{max}: Time to peak serum concentration; $t_{0.5(ab)}$: Absorption half-life; $t_{0.5(el)}$: Elimination half-life; MAT: Mean absorption time; F: Fraction of drug absorbed systemically after IM injection IBD interval between doses.C_{max}: Maximum milk concentration; t_{max}: Time to peak milk concentration; $t_{0.5(el)}$: Elimination half-life; AUC_{milk}: Area under the milk concentration-time curve from zero to infinity; AUC_{milk}/AUC_{serum}: The ratio of penetration of the drug from the blood into milk; $C_{max\text{-}milk}/C_{max\text{-}serum}$: The ratio of penetration of the drug from the blood into milk

Table 3: Milk concentrations of ceftazidime (Mean±SE) in healthy and mastitic goats following a single IV and IM administrations at a dose rate of 10 mg kg^{-1} b.wt. (n = 5)

	IV		IM	
Time (h)	Healthy	Mastitic	Healthy	Mastitic
0.5	0.48±0.09	0.55±0.10	0.25±0.04	0.50±0.08
1	0.65±0.06	1.05±0.10*	0.40±0.07	1.00±0.10**
2	0.85±0.07	2.10±0.15**	0.65±0.12	2.08±0.25**
4	0.65±0.08	1.70±0.18**	0.50±0.06	1.60±0.18**
6	0.40±0.06	1.20±0.13**	0.35±0.08	1.15±0.16**
8	0.25±0.03	0.75±0.09**	0.25±0.06	0.80±0.11**
10	0.15±0.01	0.35±0.04**	0.20±0.01	0.50±0.06**
12	ND	0.14±0.01	0.16±0.01	0.30±0.04*
24	ND	ND	ND	0.17±0.01
48	ND	ND	ND	ND

*p<0.05, ** p<0.01. ND: Not detected

AUC_{milk}/AUC_{serum} and $C_{max\text{-}milk}/C_{max\text{-}serum}$ ratios indicated a wide penetration of ceftazidime from the blood stream to the mammary gland of mastitic goats than healthy goats after intravenous and IM routes, respectively.

DISCUSSION

The use of naturally infected mastitic goats for studying the pharmacokinetics/pharmacodynamics integration of ceftazidime enables the assessment of the relevant parameters in diseased condition as those encountered clinically in the field. Following IV administration of ceftazidime (10 mg kg^{-1}) in healthy and mastitic goats, the drug concentration time data for each animal was best fitted individually using a two-compartment open model. A similar kinetic profile was recorded in sheep (Rule *et al*., 1991), cows (Rule *et al*., 1996), rabbit (Abd-El-Aty *et al*., 2001) and cats (Albarellos *et al*., 2008). Serum concentrations were lower in healthy goats as compared with mastitic animals. This could be attributed to a more rapid extravascular distribution of ceftazidime in healthy than mastitic goats. The reported long $t_{0.5\beta}$, lower Cl_{tot} and Vd_{ss} in mastitic goats is consistent with the observed higher serum concentrations of ceftazidime. In this respect, clearance of enrofloxacin was lower in pigs experimentally infected with *E. coli* (Zeng and Fung, 1997) or injected with endotoxin (Post *et al*., 2003) compared with healthy pigs. The $t_{0.5\beta}$ of ceftazidime were 2.16 h and 2.68 h in healthy and mastitic goats, respectively. These values are relatively similar to that reported in calves (2.30 h) by Soback and Ziv (1989) and rabbits (2.22 h) by Abd-El-Aty *et al*. (2001). Endotoxin (lipopolysaccharide) reduces the content and the activity of cytochrome p-450 which metabolize the drugs (Van Miert, 1990). Endotoxin produces direct tubular cell injury as well as some functional changes in the kidney, including a decrease in the renal blood flow and glomerular filtration rate and changes the intra-renal hemodynamics (Jernigan *et al*., 1988). In addition, endotoxin causes metabolic acidosis and reduces urinary pH in febrile animals

(Van Miert, 1990). It is probable that the decrease in glomerular filtration rate and metabolic acidosis induced by endotoxin plays an important role in the reduction of body clearance of ceftazedime and consequently increases its $t_{0.5\beta}$ and MRT (Waxman *et al*., 2003).

Moreover, it has been observed that endotoxin produces an increase in tubular re-absorption and a decrease in tubular secretion of some drugs. The increase in drug re-absorption could be the result of its binding to negatively charged phospholipids in the renal brush border membrane surface, by the presence of negatively charged endotoxin or lipid A. Some drugs appear to share a common transport system with endotoxin or lipid A in the tubular cells and therefore endotoxin induced reduction in tubular secretion is likely to be caused by competition for renal uptake at the basolateral membrane of tubular cells (Hasegawa *et al*., 1999).

After IM injection, the mean serum concentrations of ceftazidime were significantly higher in mastitic goats, The $t_{0.5el}$, MRT and C_{max} were higher in mastitic goats (3.05 h, 5.19 h, 9.50 μg mL^{-1}) than in healthy ones (2.11 h, 3.41 h, 6.58 μg mL^{-1}), respectively. Our result is consistent with those previously reported in un-weaned calves (Soback and Ziv, 1989) and rabbits (Abd-El-Aty *et al*., 2001).

The systemic bioavailabilities of ceftazidime after IM injection were 81.43 and 83.94% in healthy and mastitic goats, respectively. These values are similar to those reported in domestic cat (82.47%) (Albarellos *et al*., 2008) whereas it is higher than that recorded in cows (77.1%) (Rule *et al*., 1996).

The capacity of ceftazidime to bind with serum proteins was 9.05 and 12.62% in healthy and mastitic goats, respectively. This is in accordance with the corresponding values of 9-22% in rats (Mimoz *et al*., 2000; Bakker-Woudenberg *et al*., 2006) and similar to 13.3-21.6% in rabbits (Abd-El-Aty *et al*., 2001). This low degree of protein binding will not inhibit the distribution of the drug to the interstitial fluid (the site of action for most antibacterial drugs).

Significant differences were found between the pharmacokinetics of ceftazidime in healthy and mastitic goats. The concentrations of ceftazidime were higher at every point and AUC bigger when fever was induced, because of a decrease in elimination. The inflammation of the mammarygland leads to vascular permeability changes and differencesin milk composition so these factors could modify thepharmacokinetics of drugs (Gehring and Smith, 2006).

For therapy of systemic mastitis to be useful, effective passageof the drug from blood to the foci of infection must be achieved.The extent to which a drug has access into milk when given systemicallydepends on its main pharmacokinetic properties: lipid solubility,degree of ionization and extent of binding to serum and udderproteins (Ziv, 1980). The AUC_{milk}/AUC_{serum} and $C_{max\text{-}milk}/C_{max\text{-}serum}$ ratios indicated a wide penetration of ceftazidime from the blood stream to the mammary gland of mastitic goats than healthy goats after intravenous and IM routes, respectively. The MIC of the drug was 0.25 μg mL^{-1} for *E. coli* isolated from the mastitic goats. The obtained results for surrogate markers of antimicrobial activity (C_{max}/MIC and AUC/MIC) indicate the excellent pharmacodynamic characteristics of the ceftazidime in mastitic goats with *E. coli* which can be expected to optimize the clinical efficacy and minimize the development of resistance. Ultimately, ceftazidime could have been successful against susceptible mastitic pathogens in goats after parenteral administration.

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