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# PHARMACOKINETICS OF CEPHALEXIN IN LACTATING GOATS

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## SUMMARY

Pharmacokinetics of cephalexin following intravenous and intramuscular administration of 40 mg $kg^{-1}$ were carried out in a cross over study with 15 days interval using 4 female lactating goats. After intravenous adiministration the serum concentration time curve of cephalexin was best fitted using two compartements open model, with elimination half life $t_{(1/2\beta)}$ of 0.79 ± 0.12 hours, Volume of distribution at steady state $Vd_{(ss)}$ was 0.32 ± 0.04 $1kg^{-1}$ and total body clearence ($CL_B$) was 9.16 ± 1.6ml/h/kg. After intramuscular (i.m) administration, the drug was rapidly absorbed with an absorption half life ($t_{1/2ab}$) of 0.129 ± 0.012 hour, maxium serum concentration ($C_{max}$) was 32.9 ± 2.2 ug ml-1 which attained at ($T_{max}$) 0.41 ± 0.012 hours and the drug was eliminated with a half life ($t_{1/2el}$) of 0.85 ± 0.062 hour. The systemic bioavailability (F) after i.m administration was 73 ± 5.54 %. The serum protein binding tendency was 16-22 ± 2.43 %. Following i.m administration of the drug, urine concentrations were exceeding the minimum inhibitory concentrations ($MIC_{90}$) for all pathogens responsible for urinary tract infections in goats for 10 hours. The drug was detected at low concentrations in milk of lactating goats. From the aforementioned results, cephalexin could be used for treatment of urinary tract infections in goats at a dose of 40 mg $kg^{-1}$ every 10 hours.

## INTRODUCTION

Cephalexin, a broad spectrum first generation cephalosporins is active against a variety of Gram positive, Gram negative and anaerobic bacteria including Streptococcus spp., Staphylococcus spp., Escherichia coli, Klebsiella spp., Pasteurella spp. and Corynebacterium spp. (Shadomy et al., 1997 ; Silver et al., 1977). It combines resistance to the action of penecillinase produced by Staph. aureus

(Muggleton, 1968), and activity against majority of ampicillin, aminoglycosides and chloramphinicol resistant Escherichia coli strains. Streptococcus spp., Staphylococcus spp., Escherichia coli, Klebsiella spp., Pasteurella spp. and Corynebacterium spp constitutes the main Bacterial isolates from various bacterial infections (respiratory tract, urinary tract infections; abscesses) in goats (Brogden, et al., 1988; Sing et al., 1992).

Cephalexin has been used successfully for treatment of respiratory tract, urinary tract infections and abscesses in dogs (Harpster, 1981; Ling and Ruby, 1983). In addition, the excellent antibacterial spectrum, low cost and the relative stability of cephalexin against β-lactamase enzymes make it very attractive to be used in treatment of such conditions in goat. However, pharmacokinetics data for cephalexin in goat is not available. The purpose of this study was to determine the pharmacokinetics of cephalexin following i.m and intravenous administration as well as its concentrations in urine and milk of goat following intramuscular route.

## Material and Methods

### Drug:

Cephalexin sodium (Ceporex, Glaxo, UK) was diluted to final concentration of 10% with distilled water.

### Animals:

Four non pregnant, lactating Baladi goats weighing 25 to 30 kg and aged 3 ñ 4 years were used. They were housed in hygenic animal pens. All animals were clinically healthy by physical examination. They were maintained on concentrate, green and dry fodder and were provided water ad libitum.

### Experimental design:

Animals were injected intravenously and intramuscularly with cephalexin sodium in a cross over study with 15 days washout period to ensure complete clearance of the drug. The drug was given at a dose level of 40 mg $kg^{-1}$ b.wt. Intravenously via jagular vein and intramuscularly deeply into gluteal muscle. Blood samples were collected at 5, 10, 15, 30 minutes and 1, 2, 4, 6, 8, 10 and 12 hours post administration. Blood samples were centrifuged at 3000 rpm for 10 minutes and the serum was decanted and frozen at - 10°C until assayed.

Urine samples were collected before and after 15, 30 minutes and 1, 2, 4, 6, 8, 10 and 12 hours of intramuscular administration using a rubber ballon folley catheter (19 f1 $ch^{-1}$, Folatex Notra). The bladder was emptied completely before administration of the drug and irrigated with 50 ml of potassium perminganate solution $5000^{-1}$ after completion of urine sampling. Milk samples (5 ml from each udder half were collected at 1, 2, 4, 6, 8, 10 and 12 hours after i.m administration of the drug. Urine and milk samples were stored under deep freezing (-20°C) until assayed.



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**Estimation of Cephalexin concentration:**

Concentration of cephalexin in serum, urine and milk samples were determined using microbial assay method using Muller Hinton agar medium and Micrococcus luteus ATCC 9341 as the test organism (Bennet et al. 1966). Standard curves were prepared in antibiotic free goat serum, milk and urine. The standard curves for serum, milk and urine were linear using concentrations between 0.1 and 25 μg $ml^{-1}$ of cephalexin with a correlation coefficient of 0.980. The minimal inhibitory concentration for the assay method was 0.1 μg $ml^{-1}$. Serum protein binding tendency values were determined in vitro according to method of Craig and Suh (1980). Different concentrations of cephalexin (1.56, 3.12, 6.25, 12.5 and 25 μg $ml^{-1}$) in antibiotic free goat serum and phosphate buffer (pH 8) were used.

**Pharmacokinetic and statistical analysis:**

Serum concentrations versus time curves were generated and best fitted by the aid of a computer polyexponential curve stripping program (R Strip, Micromath, Scientific Software, USA).

The analytical model was selected by the application of Akaike information criterion to minimize the residuals Yamaoka et al. (1978). Data from each animal were fitted individually, the pharmacokinetic variables were computed by the aid of software program. The hybrid rate constants of distribution and elimination. Phase (α, β), first order absorption and elimination rate constants ($K_{ab}$ ; $K_{el}$ ) and the corresponding extrapolated zero time intercepts (A; B), absorption, distribution and elimination half lives ($t_{1/2ab}$, $t_{1/2}\alpha$ and $t_{1/2el}$). Distribution rate constants ($K_{12}$,$K_{21}$), mean absorption time (MAT), maximum serum concentration ($C_{max}$) and the time to be achieved ($T_{max}$). The elimination rate constant ($K_{10}$), volume of central compartment ($V_c$), parent volume of distribution at steady state ($Vd_{ss}$)and total body clearance ($CL_B$) were calculated according to Baggot (1978). Area under the serum concentration time curves was calculated by the trapezoidal rule according to Gibaldi and Perrier (1982). Standard errors were calculated from the mean data according to Snedecor and Cochran (1976).

**RESULTS**

After intravenous administration of cephalexin, serum concentrations time curve of the drug was decreased in a biphasic manner, as characterized by a 2 compartments open model. Figure 1 illustrates the mean serum concentrations as a function of time. The pharmacokinetic parameters for cephalexin following intravenous administration were recorded in table 1. The distribution half-life ($t_{1/2\alpha}$) was 0.16 hour and elimination half-life ($t_{1/2\beta}$)( was 0.79 hours. The $Vd_{ss}$ was 0.32 l $kgl^{-1}$ and PRT was 0.579 hour. Following intramuscular administration, mean serum concentrations versus time curve (Fig. 1) was best fitted by 1 compartment modeling with first order absorption. The absorption half-life ($t_{1/2ab}$) was 0.12

**Table(1):** Pharmacokinetic parameters (Mean ± SEM) of cephalexin in lactating goats following intravenous administration of 40 mg $kgl^{-1}$ (n=4).

| Parameters | Unit | Mean ± SEM |
|---|---|---|
| $Cp^{\circ}$ | $\mu g\ ml^{-1}$ | 210 ± 20.5 |
| B | $\mu g\ ml^{-1}$ | 23.1 ± 0.95 |
| β | $h^{-1}$ | 0.86 ± 0.04 |
| $T_{1/2\beta}$ | h. | 0.79 ± 0.12 |
| A | $\mu g\ ml^{-1}$ | 187 ± 8.51 |
| α | $h.^{-1}$ | 4.16 ± 0.26 |
| $T_{1/2\alpha}$ | h. | 0.16 ± 0.07 |
| $K_{12}$ | $h.^{-1}$ | 0.86 ± 0.06 |
| $K_{21}$ | $h.^{-1}$ | 1.23 ± 0.09 |
| $K_{el}$ | $h.^{-1}$ | 2.93 ± 0.34 |
| Vc | $Lkg.^{-1}$ | 0.19 ± 0.09 |
| $Vd_{ss}$ | $Lkg.^{-1}$ | 0.32 ± 0.04 |
| $CL_B$ | ml/kg/min. | 9.16 ± 1.60 |
| $AUC_{i.v.}$ | µg/ml/h | 71.5 ± 6.71 |
| AUMC | µg/ml/h | 4.46 ± 0.65 |
| MRT | h. | 0.57 ± 0.06 |

$Cp^{\circ}$ A, B, zero-time intercepts of the biphasic dispositon curve ($Cp^{\circ}$ = A + B); hydrid rate constants representing the slopes of distribution and elimination phases, respectively, $t_{1/2\alpha}$ distribution half-life $t_{1/2\beta}$, elimination half-life; MRT, mean residence time; Vc, apparent volume of the central compartment; $Vd_{ss}$, volume of distribution at steady state; $K_{21}$, first-order rate constant for transfer from peripheral to central compartment; $K_{12}$, first-order rate constant for transfer from contral to peripheral compartment; $K_{10}$,elimination rate constant; AUMC, area under the first moment curve; AUC, area under curve; $Cl_{\beta}$, total body clearance



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**Table (2):** Pharmacokinetic parameters (Mean ± SEM) of cephalexin in lactating goats following intramuscular administration of 40 mg $kg^{-1}$ (n=4).

| Parameters | Unit | Mean ± SEM |
|---|---|---|
| A | $\mu g\ ml^{-1}$ | 51.3 ± 7.56 |
| $K_{ab}$ | $h^{-1}$ | 5.35 ± 0.43 |
| $T_{1/2(ab)}$ | h | 0.12 ± 0.01 |
| B | $\mu g\ ml^{-1}$ | 34.9 ± 4.30 |
| $K_{el}$ | $h.^{-1}$ | 0.80 ± 0.04 |
| $T_{1/2el}$ | h. | 0.85 ± 0.06 |
| $C_{max}$ | $\mu g\ ml^{-1}$ | 32.9 ± 2.28 |
| $T_{max}$ | h | 0.41 ± 0.01 |
| AUC | $\mu g\ ml^{-1}.h$ | 51.8 ± 4.90 |
| MRT | h | 1.04 ± 0.08 |
| AUMC | $\mu g\ ml^{-1}.h$ | 55.2 ± 6.70 |
| MAT | h | 0.46 ± 0.02 |
| Ibd | h | 6.30 ± 1.30 |
| F | % | 73.0 ± 5.54 |

$K_{ab}$, first-order absorption rate constant; $t_{1/2(ab)}$, absorption half-life; MAT, mean absorption time; $K_{el}$, first-order elimination rate constant; $t_{1/2el}$, elimination half-life; $C_{max}$, maximum serum concentration after intramuscular administration; $T_{max}$, time to peak serum concentration; F, systemic bioavailability following intramuscular administration; Ibd, interval between doses.

**Table(3):** Urine and milk concentrations ($\mu g\ ml.^{-1}$) of cephalexin in lactating goats following intramuscular administration of 40 mg $kg.^{-1}$ (n=4).

| Time (hours) | Mean ± SEM | |
|---|---|---|
| | Milk | Urine |
| 0.5 | 0.26 ± 0.01 | 779 ± 80.61 |
| 1 | 0.42 ± 0.02 | 648 ± 69.32 |
| 2 | 0.53 ± 0.06 | 534 ± 57.66 |
| 4 | 0.22 ± 0.02 | 312 ± 28.27 |
| 6 | 0.16 ± 0.09 | 180 ± 43.13 |
| 8 | B | 61.5 ± 16.20 |
| 10 | B | 29.7 ± 4.60 |
| 12 | B | 4.60 ± 0.95 |

B = Below the limit of detection.



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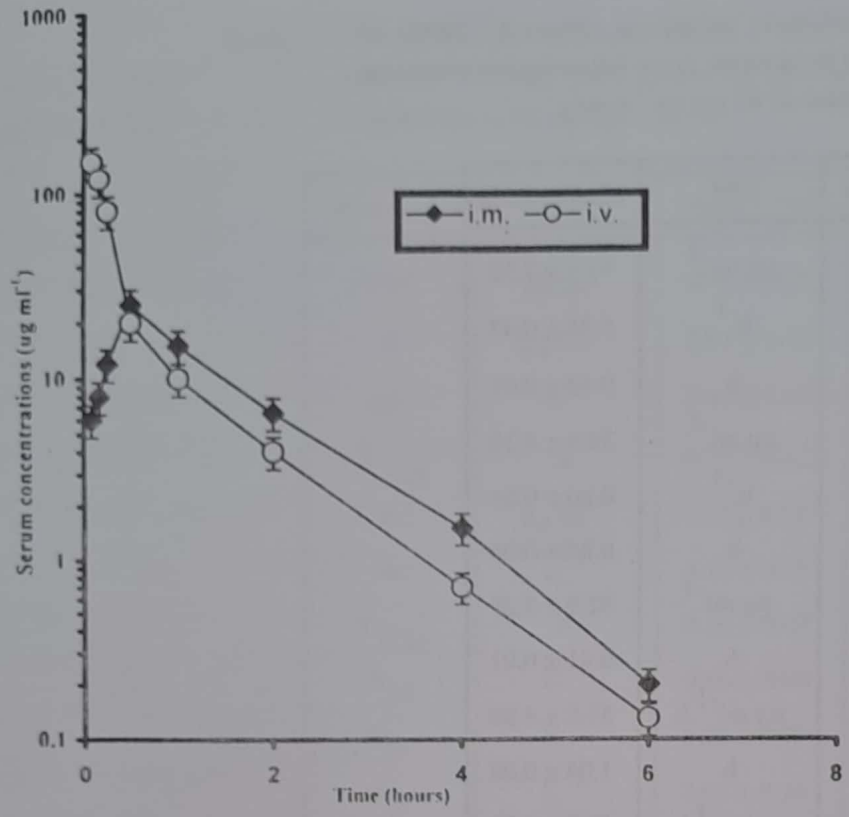


Fig.(1): Semi-logarithmic graph depicting the time-concentrations course of cephalexin in goats following intravenous and intramuscular administration of 40 mf $kg^{-1}$ body weight (n=4)

hour and elimination half life ($t_{1/2\beta}$) was 0.85 hour (Table 2). Maximum serum concentration was 32.9 µg $ml^{-1}$, achieved at 0.41 hour. The concentrations of the drug after 8 hours of i.v and i.m administration were lower than the minimal limit of sensitivity for the assay method used.

The MRT and MAT were 1.04 and 0.46 hour, respectively. Protein binding tendency of cephalexin was 16-22 ± 2.43 %. Cephalexin was detected in goats urine for 12 hours (Table 3) post intramuscular administration .The highest concentration in urine was (779 µg $ml^{-1}$) achieved at $^1/_2$ hour. The concentrations of cephalexin in milk were low (Table 3), within the range of 0.16-0.53 µg $ml^{-1}$ .

## DISCUSSION

Following intravenous administration of cephalexin in goats, serum concentrations versus time curves were best described using two compartments open model. Similar finding was reported for cephalexin in calve, cow and dog (Soback et al., 1987; Garg et al., 1996; Carli et al., 1999). Cephalexin was rapidly distributed with $t_{1/2\alpha}$ of 0.16 hour. This value was close to those reported for cephalexin in calve and dog 0.16 hour (Carli et al., 1983; 1999). The drug was rapidly eliminated with $t_{1/2\beta}$ of 0.79 hour. This value was shorter than values reported in calves (1.03 hour) by Carli et al. (1983), in cow (1.16 hour) by Soback et al. (1988) and in dog (1.38) by Carli et al. (1999)

Volume of distribution $Vd_{ss}$ was lower than one (0.32 $l.kg^{-1}$) indicated poor distribution of the drug. This value was close to the values previously reported by Soback et al. (1988) in cow (0.39 $l.kg^{-1}$), Garg et al. (1990) in buffalo calves (0.46 $l.kg^{-1}$) and Carli et al. (1999) in dog (0.21 $l.kg^{-1}$). The reported total body clearance ($CL_{\beta}$) in this study (9.16 ml/min/kg) was close to the value previously reported in cow (10.5 ml/min/kg) by Soback et al. (1988) but higher to the value reported in dogs (2.5 ml/min/kg) this difference could be attributed to the effect of renal tubular reabsorption of acidic drugs that occurred mainly in acidic urine of dogs (Carli et al., 1999).

Following intramuscular administration of cephalexin, the drug was rapidly absorbed with a $t_{1/2ab}$ of 0.129 hour and MAT of 1.04 hour, rapid absorption of cephalexin was consistent with findings of Soback et al. (1988) in cow and sheep but it was differed from findings (0.86 hour) reported in dogs by Carli et al. (1999), which suggested slow absorption of the drug from the site of injection. However slow absorption ($t_{1/2ab}$: 0.38 hour) has been previously reported for other cephalosporins (cefotaxime) in dogs (Guerrini et al., 1986). Such difference in rate of drug absorption between species could be explained on the fact that each species has its own hemodynamic characters (Caprile, 1988). Time to peak serum concentration was 0.41 hour, this value was close to the value previously reported in cow (0.33 hour) by Soback et al. (1988) but differed from the values reported in dogs (0.9 hour) and cats (0.7 hour) by Silley et al. (1988). The terminal elimination half life reported in this study (0.85 hour) was shorter than the value reported in calve (1.16 hour) by Soback et al. (1987) but longer than the corresponding one in cow (0.76 hour) reported by Soback et al. (1988). The systemic bioavilability following i.m administration reported in this study (73%) was identical to the value reported in calve by Carli et al. (1983) even though, it was differed from values reported in buffalo calve and cow calve (67 and 81%) by Garg et al. (1992).

The minimal inhibitory concentrations ($MIC_{90}$) of cephalexin for 90% of the field isolates of gram positive pathogens are within 0.2-1 $\mu g\ m^{-1}$ (Shadomy et al., 1977) whereas, for gram negative bacteria the values are 2-8 $\mu g\ ml^{-1}$. Following intramuscular injection, serum concentrations of cephalexin higher than the $MIC_{90}$ for gram positive and gram-negative bacteria were maintained for 5 and 2 hours, respectively. Therefore, cephalexin might be usefull for treatment of bacterial infections (abscess) caused by gram-positive pathogens only, but such use is not practical for treatment of infections caused by gram negative pathogen.

In human, the urinary recovery of cephalexin accounts for about 95 % of the dose and the drug is cleared from the kidneys mainly by glomerular filtration combined with active tubular secretion (Barbhaiya, 1996). Since no metabolites have

been identified in human for cephalexin (Nightingale et al., 1975), the renal and total body clearance would be expected to be identical. In the present study the mean value of total body clearance (9.16 ml/ min/kg) was higher than the glomerular filtration rate of endogenous creatinine (2.2 ml/min/kg) previously reported for goats (Nawaz and Rasmussen 1979; Akhtar et al., 1997) and suggesting the involvement of both glomerular and tubular secretion in the process of renal excretion of the drug. These results supported earlier findings by Welles et al., (1968) who reported that, concurrent probencid administration significantly altered excretion of cephalexin. Following i.m administration, the urine concentrations of cephalexin were exceeding the $MIC_{90}$ for gram negative and gram positive bacteria for 10 hours. The reported results recommended the use of cephalexin in treatment of urinary tract infections in goats caused by susceptible pathogens.

The concentrations of cephalexin in milk were very low suggesting poor penetration of the drug from the serum to milk. The extent of passive diffusion of the drug from the serum into the udder is dependant on its physico-chemical properties, ultimately their pka value (Ziv, et al., 1973). Cephalexin is a weak acidic drug (pka; 4). Large percentage of the drug is ionized in the serum. The ionized part of the drug has low lipid : water partition coefficient so it is poorly penetrate into the milk. As a result of poor penteration of cephalexin into milk of lactating goats, cephalexin at a dose of 40 mg $kg^{-1}$ might be useful in treatment of urinary tract infections caused by susceptible pathogens especially in lactating goats, so as to minimize the milk withholding time accompained treatment of such conditions, comparable to other antibiotics those achieve higher concentrations in milk and need a longer milk withholding time. In addition, these results indicated that systemic administration of cephalexin for treatment of mastitis in goats is impractical.

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