PHARMACOKINETICS OF CEFOTAXIME IN GOATS FOLLOWING MULTIPLE DOSING

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ABSTRACT
Objective to study the pharmacokinetic parameters of cefotaxime after repeated intramuscular injections in normal and experimentally Salmonella typhimurium infected goats. Cefotaxime was given at dose rate of 50 mg/kg b wt. three times daily for five consecutive days Plasma, milk and urine samples were collected. Cefotaxime level were estimated by microbiological assay. Plasma concentration revealed a lower significant concentration at all time sampling in Salmonella typhimurium infected goats than in normal goats. Maximum plasma concentration [C_{\text{max}}] was significantly increase in normal than Salmonella typhimurium infected goats. Cefotaxime was cleared by all clearance processes (Cl_{\text{tot}}) in the body at significant faster rates in Salmonella typhimurium infected goats than in normal goats. The highest concentrations of cefotaxime in milk were recorded 4 hours after each intramuscular dose with a significant lower value in Salmonella typhimurium infected goats than in normal goats. The mean peak urine concentrations of cefotaxime were reached 2 hours after each intramuscular dose with a lower significant concentration in Salmonella typhimurium infected goats than in normal goats. The study indicated that cefotaxime was useful for treatment of Salmonella typhimurium infections.

Key words: Pharmacokinetics, Cefotaxime, Goats.

INTRODUCTION
Recently, goats became an important aspect of animal production in Egypt. A large number of rural households raise goats comprising more than 90% of total goat population in Egypt. This goat herds contribute to improve the standard of living of the rural people through supplying them by offspring, mohair and milk (Hamed et al., 2009).

Cefotaxime has broad antibacterial spectrum and is mainly active against Gram-negative bacteria especially on Entrobacteriaceae including Salmonella spp, Escherichia coli, Enterobacter species, Citrobacter freundii, Serratia marcescens, Morganella morganii, and

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Protus vulgaris, Haemophilus influenza, Neisseria gonorrhoeae and Bacteroides fragilis were susceptible to this drug. Also it acts on gram positive bacteria as staphylococcus aureus, non enterococcal streptococci. (Jones and Thornsberry, 1982) and (Neu, 1982).

Cefotaxime is widely used and most prescribed drug due to the antimicrobial spectrum, therapeutic efficacy and low adverse effect. (Barbarin et al., 2001 and Eidalo et al., 2004).

The aim of present work was undertaken to study the pharmacokinetic parameters of cefotaxime after repeated intramuscular injection in normal and experimentally Salmonella typhimurium infected goats.

MATERIAL AND METHODS
Drug
Cefotaxime was used in this study under the trade name (Claforan®) Claforan® available as glass vial containing 1048 mg cefotaxime sodium equivalent to
1000 mg cefotaxime. Claforan® was produced by Sanofi Egypt s.a.e. under license of Aventis/France.

Experimental animals and design
Four clinically normal lactating baladi and four experimentally Salmonella typhimurium infected lactating goats were used in this investigation. The body weight and age of the tested goats ranged from 21–30 kg.b.wt. and from 2 to 3 years old (for normal goats) and from 23 – 31 kg.b.wt. and from 2.5 to 3.5 years old (for experimentally Salmonella typhimurium infected goats). They were housed in hygienic stable fed on barseem, drawa and concentrate and water was provided ad-libitum.

Group (1)
It included 4 post-partum lactating goats. Each goat was injected intramunulary into the gluteus medius muscle with 50 mg cefotaxime per kilogram body weight, three times daily for five consecutive days.

Group (2)
It included 4 experimentally Salmonella typhimurium infected post-partum lactating goats. Each goat was injected intramuscularly into the gluteus medius muscle with 50 mg cefotaxime per kilogram body weight, 48-72 hours after experimental infection with Salmonella typhimurium three times daily for five consecutive days.

Collection of samples
Blood samples
Three ml blood samples were collected from right jugular vein following intramuscular injection of cefotaxime in normal goats. Blood samples were collected after 0.083, 0.167, 0.25, 0.50, 1, 2, 4 and 8 following first intramuscular dose. Blood samples following the second, third, fourth and fifth intramuscular doses were collected at 0.50, 1 , 2 , 4 , 6 and 8 hours post injection. Blood samples from goats were collected with anticoagulant (EDETA) and plasma was separated by centrifugation, collected and divided into two parts, the first part was used for assay of cefotaxime and the second part was used for creatinine assay. All plasma samples were stored at -20°C until assay for cefotaxime and creatinine.

Milk samples
The udder was completely evacuated before drug administration and milk samples were collected by hand stripping from both teats. Milk samples were taken after 0.50, 1, 2, 4, and 8 hours of administrations. Milk samples taken at 0.25 h were discarded. Milk samples from goats of all groups were centrifuged. The skimmed milk was collected and stored at -20°C until assay for cefotaxime.

Analytical Procedure
Assay of cefotaxime
Cefotaxime was assayed in plasma, distilled water and milk by microbiological method. Using Escherichia-coli (ATCC25922) as tested organism (Arret et al., 1971).

Preparation of microbial suspension of Salmonella typhimurium for experimental infection
Salmonella typhimurium obtained from Microbiological department (animal Health Institute, Dokky, Giza, Egypt).

Pharmacokinetic analysis
The pharmacokinetic parameters were calculated by using Winonlin, version 2.1 and other parameters according to Baggot (1978a & b).

Statistical Analysis:
The data were calculated as mean ± standard error. All statistical analysis was carried out by using the SPSS program (one-Sample T-Test).The effects of tested drug on the studied parameters were compared with the control by the Student’s (t) test.

RESULTS
The pharmacokinetic parameters of cefotaxime after repeated intramuscular injection in normal and Salmonella typhimurium infected goats are reported in (Table 1 and Figure 1). A & B, Zero time plasma drug concentration intercepts of biphasic intravenous disposition curve. The coefficient B is based on the terminal exponential phase (μg/ml); α & β, Hybrid rate constant of biphasic intravenous disposition curve values of α and β are related to the slopes of distribution and elimination phase respectively, of biexponential drug disposition curve (h-
1); AUC, Total area under the serum drug concentration versus time curve from $t = 0$ to $t = \alpha$ after administration of a single dose; $C^0$. Drug concentration in the serum at zero time immediately after a single intravenous injection ($\mu$g/ml); $C_{\text{max}}$, Maximum serum concentration of drug in blood after extra vascular administration ($\mu$g/ml); $C_{\text{tot}}$, The total clearance of a drug, which represents the sum of all clearance processes in the body (ml/kg/min);

Kab, Apparent first order absorption rate constant (h⁻¹); $K_{\text{el}}$, First - order elimination rate constant for disappearance of drug from central compartment (h⁻¹); $t_{0.5(\text{ab})}$, The absorption half- life (h); $t_{0.5(\alpha)}$, Distribution half - life (h); $t_{0.5(\beta)}$, Elimination half - life (h); $t_{\text{max}}$, The time at which the maximum concentration of drug was reached after extravascular administration (h)); Vdss, The apparent volume of distribution.

Table 1. Pharmacokinetic parameters of cefotaxime after repeated intramuscular injection of 50 mg/kg b.wt. three times daily of cefotaxime for five consecutive day in normal (N) and experimentally *Salmonella typhimurium* infected (I) goats (n=4).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>First</th>
<th>Second</th>
<th>Fourth</th>
<th>Fifth</th>
<th>Seventh</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (X±S.E.)</td>
<td>I (X±S.E.)</td>
<td>N (X±S.E.)</td>
<td>I (X±S.E.)</td>
<td>N (X±S.E.)</td>
</tr>
<tr>
<td>$C^0$</td>
<td>$\mu$g/ml</td>
<td>38.15±0.954</td>
<td>14.97±0.629</td>
<td>36.12±0.994</td>
<td>14.97±0.629</td>
<td>39.14±0.979</td>
</tr>
<tr>
<td>$A$</td>
<td>$\mu$g/ml</td>
<td>18.38±0.726</td>
<td>9.66±0.242</td>
<td>23.38±0.726</td>
<td>9.66±0.242</td>
<td>12.73±0.522</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>h⁻¹</td>
<td>0.10±0.021</td>
<td>0.35±0.041</td>
<td>0.98±0.034</td>
<td>0.21±0.041</td>
<td>0.817±0.034</td>
</tr>
<tr>
<td>$t_{0.5(\text{ab})}$</td>
<td>h</td>
<td>0.47±0.006</td>
<td>0.51±0.008</td>
<td>0.60±0.009</td>
<td>0.51±0.008</td>
<td>0.58±0.009</td>
</tr>
<tr>
<td>$K_{\text{el}}$</td>
<td>h⁻¹</td>
<td>1.69±0.022</td>
<td>1.78±0.057</td>
<td>1.52±0.022</td>
<td>1.78±0.057</td>
<td>1.48±0.058</td>
</tr>
<tr>
<td>$t_{0.5(\alpha)}$</td>
<td>h</td>
<td>0.41±0.005</td>
<td>0.38±0.016</td>
<td>0.45±0.019</td>
<td>0.45±0.019</td>
<td>0.45±0.007</td>
</tr>
<tr>
<td>$T_{\text{max (cal)}}$</td>
<td>h</td>
<td>1.05±0.013</td>
<td>1.01±0.037</td>
<td>1.08±0.015</td>
<td>1.08±0.015</td>
<td>1.06±0.040</td>
</tr>
<tr>
<td>$C_{\text{max (cal)}}$</td>
<td>$\mu$g/ml</td>
<td>12.03±0.257</td>
<td>4.06±0.138</td>
<td>13.89±0.217</td>
<td>4.06±0.138</td>
<td>4.21±0.153</td>
</tr>
<tr>
<td>$B$</td>
<td>$\mu$g/ml</td>
<td>19.77±0.257</td>
<td>5.31±0.186</td>
<td>19.42±0.303</td>
<td>5.31±0.186</td>
<td>6.36±0.167</td>
</tr>
<tr>
<td>$\beta$</td>
<td>h⁻¹</td>
<td>0.20±0.004</td>
<td>0.20±0.009</td>
<td>0.20±0.010</td>
<td>0.20±0.009</td>
<td>0.20±0.009</td>
</tr>
<tr>
<td>$t_{0.5(\alpha)}$</td>
<td>h</td>
<td>2.26±0.029</td>
<td>2.59±0.093</td>
<td>2.39±0.034</td>
<td>2.59±0.093</td>
<td>2.67±0.010</td>
</tr>
<tr>
<td>$Cl_{\text{int.}}$</td>
<td>ml/kg/h</td>
<td>6.80±0.08</td>
<td>20.56±0.925</td>
<td>6.66±0.079</td>
<td>13.27±0.504</td>
<td>6.19±0.075</td>
</tr>
<tr>
<td>AUC</td>
<td>$\mu$g/ml</td>
<td>56.92±0.740</td>
<td>18.61±0.726</td>
<td>61.62±0.924</td>
<td>18.61±0.726</td>
<td>25.47±0.990</td>
</tr>
<tr>
<td>$C^0$</td>
<td>$\mu$g/ml</td>
<td>39.79±0.955</td>
<td>23.60±1.16</td>
<td>43.63±1.13</td>
<td>23.60±1.16</td>
<td>25.58±1.20</td>
</tr>
<tr>
<td>$A$</td>
<td>$\mu$g/ml</td>
<td>14.63±0.670</td>
<td>15.37±0.734</td>
<td>18.31±0.677</td>
<td>15.37±0.734</td>
<td>15.92±0.780</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>h⁻¹</td>
<td>1.10±0.019</td>
<td>1.91±0.059</td>
<td>1.11±0.016</td>
<td>1.91±0.059</td>
<td>1.15±0.057</td>
</tr>
<tr>
<td>$t_{0.5(\alpha)}$</td>
<td>h</td>
<td>0.63±0.009</td>
<td>0.58±0.029</td>
<td>0.62±0.009</td>
<td>0.58±0.029</td>
<td>0.60±0.030</td>
</tr>
</tbody>
</table>

References:

K_{ab} \quad h^{-1} \quad 1.86 \pm 0.030 \quad 1.73 \pm 0.036 \quad 1.76 \pm 0.026 \quad 1.57 \pm 0.082 \quad 1.87 \pm 0.0028 \quad 1.93 \pm 0.094 \quad 2.04 \pm 0.031 \quad 1.92 \pm 0.096 \quad 2.19 \pm 0.035 \quad 1.95 \pm 0.094

\text{t_{0.5(ab)}} \quad h \quad 0.373 \pm 0.006 \quad 0.536 \pm 0.027 \quad ** \quad 0.394 \pm 0.006 \quad 0.442 \pm 0.021 \quad 0.370 \pm 0.005 \quad 0.359 \pm 0.018 \quad 0.336 \pm 0.005 \quad 0.389 \pm 0.019 \quad 0.316 \pm 0.005 \quad 0.355 \pm 0.018

T_{\text{max (cal)}} \quad h \quad 1.13 \pm 0.017 \quad 1.09 \pm 0.055 \quad 1.12 \pm 0.016 \quad 1.07 \pm 0.054 \quad 1.12 \pm 0.019 \quad 1.09 \pm 0.016 \quad 1.16 \pm 0.016 \quad 1.10 \pm 0.016 \quad 1.1 \pm 0.016 \quad 1.12 \pm 0.016

C_{\text{max (cal)}} \quad \mu g/ml \quad 18.01 \pm 0.288 \quad 6.95 \pm 0.148 \quad ** \quad 19.94 \pm 0.279 \quad 8.04 \pm 0.185 \quad ** \quad 20.48 \pm 0.328 \quad 8.25 \pm 0.245 \quad *** \quad 22.16 \pm 0.355 \quad 9.10 \pm 0.281 \quad * \quad 22.40 \pm 0.358 \quad 9.32 \pm 0.358

B \quad \mu g/ml \quad 25.16 \pm 0.403 \quad 8.23 \pm 0.300 \quad *** \quad 25.32 \pm 0.355 \quad 9.66 \pm 0.473 \quad *** \quad 26.98 \pm 0.391 \quad 11.68 \pm 0.537 \quad *** \quad 33.59 \pm 0.470 \quad 11.90 \pm 0.595 \quad *** \quad 32.92 \pm 0.461 \quad 12.03 \pm 0.565

\beta \quad h^{-1} \quad 0.240 \pm 0.004 \quad 0.255 \pm 0.013 \quad 0.222 \pm 0.003 \quad 0.249 \pm 0.013 \quad 0.237 \pm 0.013 \quad 0.265 \pm 0.004 \quad 0.241 \pm 0.012 \quad 0.246 \pm 0.012 \quad 0.238 \pm 0.012 \quad 0.272 \pm 0.012

\text{t_{0.5(b)}} \quad h \quad 2.89 \pm 0.046 \quad 2.72 \pm 0.133 \quad 3.12 \pm 0.047 \quad 2.79 \pm 0.137 \quad 2.92 \pm 0.044 \quad 2.61 \pm 0.128 \quad 2.87 \pm 0.045 \quad 2.82 \pm 0.133 \quad 2.91 \pm 0.042 \quad 2.55 \pm 0.125

\text{Cl_{tot.}} \quad ml/kg/h \quad 5.37 \pm 0.057 \quad 13.06 \pm 0.496 \quad *** \quad 5.47 \pm 0.062 \quad 13.24 \pm 0.503 \quad *** \quad 5.15 \pm 0.057 \quad 11.27 \pm 0.439 \quad *** \quad 4.34 \pm 0.051 \quad 10.68 \pm 0.416 \quad *** \quad 3.32 \pm 0.048 \quad 10.62 \pm 0.424

\text{AUC} \quad \mu g/ml/h \quad 95.61 \pm 1.43 \quad 36.23 \pm 1.78 \quad 107.92 \pm 1.73 \quad 38.09 \pm 1.91 \quad 106.61 \pm 1.81 \quad 37.61 \pm 1.88 \quad 123.61 \pm 2.06 \quad 45.54 \pm 2.18 \quad 123.34 \pm 2.03 \quad 47.32 \pm 2.22

\* P≤0.05 \quad ** P≤0.01 \quad *** P≤0.00

Figure 1. Plasma concentrations of cefotaxime after repeated intramuscular injection of 50 mg/kg b.wt. three times daily of cefotaxime in normal and experimentally Salmonella typhimurium infected goats (n=4).
DISCUSSION

In this study, the obtained results indicated that cefotaxime could be detected in a therapeutic level for 8 hours in plasma following repeated intramuscular administrations. These concentrations (1.73 µg/ml) exceeded the minimum inhibitory concentration (MIC) for sensitive Salmonella typhimurium to cefotaxime. The minimum inhibitory concentration (MIC\(_{90}\)) of cefotaxime was (0.016-1 µg/ml) (Knudsen et al., 1997) which most effective against the majority of sensitive Gram-positive and Gram-negative pathogens.

An average MIC\(_{90}\) of 1.73 µg/mL of cefotaxime has been considered. Based on this data, the intramuscular injection of cefotaxime at a dose of 50 mg/kg at 8 h interval is sufficient to maintain plasma concentration above MIC\(_{90}\) for most sensitive susceptible pathogens (g/m); these findings indicate the suitability of successful use of cefotaxime in goats. A recommended three daily dose of 50 mg/kg of cefotaxime given intramuscularly achieves therapeutic concentrations in plasma exceeding the MIC\(_{90}\) against different susceptible pathogens in goats.

The relative higher plasma concentrations of cefotaxime after the last dose compared to the first doses indicated the accumulation of cefotaxime in blood during multiple dosing at 8 hours intervals for five consecutive days. These observations agreed with data reported by El-Hewaity et al., (2014).

The obtained result was inconsistent with that reported by Inges et al., (1982) When cefotaxime was administered repetitively in patients, the ratio of maximal serum levels after the last dose to those after the first dose demonstrated minimal accumulation of intact drug and by Sharma and Srivastava et al., (2003) who found that a lack of cumulative effect after repeated intramuscular injection of cefotaxime in buffalo calves.

The study showed that the blood concentrations of cefotaxime in Salmonella typhimurium infected goats were significantly lower than those in normal goats following repeated intramuscular injection. These lower blood concentrations in Salmonella typhimurium infected goats might be attributed to the higher penetrating power of cefotaxime to the diseased tissues (Baggot, 1980). This phenomenon was similar to data recorded by Abdulgafar et al., (2011) and El-Sayed et al., (1994)

The maximum [C\(_{max}\)] and minimum plasma concentration of cefotaxime during multiple regimen in normal (12.03, 1.73 µg/ml) respectively and experimentally Salmonella typhimurium infected goats (4.06, 0.623 µg/ml) respectively, this indicated that dose regimen of 50 mg/kg b.wt every 8 hours for five days would provide effective and safe concentrations exceeded MIC for most microorganism sensitive to cefotaxime.

The highest concentrations of cefotaxime in milk were recorded 4 hours after each intramuscular injection with a significant lower value in Salmonella typhimurium infected goats than in normal goats. This might be attributed to accumulation of drug in the inflammed tissues (Baggot, 1980). This result is similar to those reported by El-sayed et al., (1989) and (1994) who found that milk concentrations of gentamicin and cephradine were significantly lower in infected goats and cattle than in normal ones, respectively.

Cefotaxime have three ionization groups: carboxylic, amide and aminothiazole (Aleksic et al., 2005), these compounds are sufficiently lipids- soluble to be able to penetrate tissues.

The study showed that, the urine concentrations of cefotaxime were greater than the concurrent plasma concentrations following intramuscular injection. This observation is similar to those reported in cows after cephalin administrations (Prades et al., 1988).

The high concentrations of cefotaxime in urine of goats are indicator for renal elimination and are considered the main route of elimination of the drug. These results consistent with those reported by Luthy et al., (1979), Nielsen et al., (1980), Inges et al., (1982), Ohkawa et al., (1983) and Matzke et al., (1985) reported that approximately 40 to 60% of cefotaxime was excreted renally in adults with normal renal function. Molinoff et al., (1996) reported that cephalosporin derivatives are generally excreted through the kidney by glomerular filtration and active tubular secretion.

In the present study, urine concentrations of cefotaxime increased with the repetition of dosing. This observation supported by Holazo et al., (1986) after repeated intramuscular administrations of ceftriaxone in healthy volunteers.

CONCLUSION

The present study concluded that:

- Plasma concentrations of cefotaxime in normal and Salmonella typhimurium infected goats could be detected in a therapeutic level for 8 hours in plasma following repeated intramuscular administrations. These concentrations exceeded the minimum inhibitory concentration (MIC) of Salmonella typhimurium to cefotaxime a factor indicating that cefotaxime is a drug of choice for Salmonella typhimurium infection.
- The high concentrations of cefotaxime in urine, suggested that cefotaxime is a suitable antimicrobial for treatment of urinary tract infections.
- The high milk concentrations of cefotaxime in lactating goats suggested that cefotaxime could be used for treatment of mastitis.
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