Pharmacokinetics and distribution of ceftazidime to milk after intravenous and intramuscular administration to lactating female dromedary camels (Camelus dromedarius)

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Objective—To determine the plasma disposition kinetics, absolute bioavailability, and milk concentrations of ceftazidime in healthy lactating female dromedary camels (Camelus dromedarius) following IV and IM administration of a single dose of 10 mg/kg (4.5 mg/lb).

Design—Prospective crossover study.

Animals—8 healthy adult lactating female dromedary camels.

Procedures—Camels received ceftazidime (10 mg/kg) IV and IM in a crossover study design with a 15-day washout period between treatments. Plasma and milk samples were collected at predetermined times for 48 hours after drug administration and analyzed by use of high-performance liquid chromatography.

Results—A 2-compartment open model best represented the plasma concentration-versus-time data after IV and IM administration of ceftazidime to camels. Plasma ceftazidime concentrations decreased biexponentially after IV administration with mean distribution and elimination half-lives of 0.3 hours and 2.85 hours, respectively. After IM administration, the mean maximum plasma concentration of ceftazidime was 32.43 µg/mL (1.21 hours after administration), mean elimination half-life was 3.20 hours, mean residence time was 4.84 hours, and mean systemic bioavailability was 93.72%. Distribution of ceftazidime from plasma to milk was rapid and extensive as indicated by the ratio of the area under the milk concentration-versus-time curve to the area under the plasma concentration-versus-time curve and the ratio of the maximum milk concentration to the maximum plasma concentration of ceftazidime after IV and IM administration.

Conclusions and Clinical Relevance—Results suggested that ceftazidime may be a useful treatment for female camels with mastitis caused by susceptible microorganisms. (J Am Vet Med Assoc 2013;243:424–429)

Ceftazidime is a third-generation cephalosporin. It is bactericidal and acts by means of binding to penicillin-binding proteins of gram-negative bacteria to inhibit the cross-linking of peptidoglycan, thereby interfering with cell wall synthesis.1

Ceftazidime is bactericidal via a time-dependent mechanism; the pharmacokinetic variable related to the efficacy of the drug is the amount of time that the serum drug concentration exceeds the MIC for a pathogen. The time that the serum concentration of a drug is greater than the MIC for a pathogen should be 40% to 60% of the interdose interval. For such drugs, circulating concentrations greater than the MIC do not result in increased efficacy against bacteria.2-5

Ceftazidime has broad-spectrum activity against gram-negative bacteria, such as Enterobacteriaceae (Escherichia coli, Proteus spp, and Klebsiella spp) and Pseudomonas aeruginosa, the efficacy of the drug against P aeruginosa is an advantage over other third-generation cephalosporins. Ceftazidime also has efficacy against various gram-positive cocci, such as Staphylococcus spp and Streptococcus spp.6 Because of the broad spectrum of antimicrobial activity of ceftazidime, we believed it would be useful for treatment of lactating female dromedary camels (Camelus dromedarius).

Mastitis in camels has zoonotic and economic importance and can have negative effects on human health and animal production.7 Infections in mammary glands of dairy camels are typically caused by bacteria. Bacteria isolated from dromedary camels with acute mastitis include Klebsiella pneumoniae, E coli, Pasteurella haemolytica, and Streptococcus agalactiae.8

Information regarding mastitis diagnosis and treatment for camels is typically adapted from information for cows. To the authors’ knowledge, no studies have been conducted to determine the pharmacokinetics and milk concentrations of ceftazidime in lactating camels. However, ceftazidime administration to camels could be a potential health hazard for humans because of persistence of drug residues in milk.
The pharmacokinetic properties of ceftazidime have been determined for animals of various species. No information is available regarding the pharmacokinetic properties of ceftazidime in camels, to the authors’ knowledge; the pharmacokinetics of cephalothin, ceftiofur, and ceftiraxone in camels have been determined. The purpose of the study reported here was to determine the plasma disposition kinetics, absolute bioavailability, and milk concentrations of ceftazidime in healthy lactating female dromedary camels following IV and IM administration of a single dose of 10 mg/kg (4.5 mg/lb).

Materials and Methods

Animals—Eight healthy female lactating camels (age range, 5 to 8 years; weight range, 390 to 510 kg [858 to 1,122 lb]) were included in the study. None of the camels had received any drugs for ≥4 months before the start of the study. Before each experiment of the study, the camels were determined to be healthy on the basis of histories and results of physical examinations. The camels were in good nutritional condition; during the study, they were fed high-quality alfalfa hay once daily and water was available ad libitum. The camels were milked twice per day. The Advisory Committee of the Faculty of Veterinary Medicine, Cairo University, Cairo, Egypt, approved the experimental protocol.

Ceftazidime administration—The study included 2 experiments performed in a crossover study design. Ceftazidime was reconstituted in sterile water to a concentration of 250 mg/mL. Ceftazidime (10 mg/kg) was administered to camels IV via the left jugular vein as a bolus or IM in left gluteal muscles. Camels received the drug via the converse route during the second experiment; the camels that had been injected IV with the drug were injected IM and vice versa. Camels underwent a 15-day washout period between treatments.

Collection of plasma and milk samples—Venous whole blood samples (5 mL) were obtained from a jugular vein of each camel into 10-mL evacuated tubes containing heparin. Blood samples were obtained immediately before administration of ceftazidime (0 hours) and 0.16, 0.33, 0.5, 1, 2, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours after that time. Blood samples were centrifuged at 3,000 X g for 15 minutes, and plasma was collected.

Milk samples (5 mL) were collected from mammary glands of camels into vials after complete evacuation of the udder (to avoid a dilution effect), immediately prior to administration of ceftazidime (0 hours), and 0.5, 1, 2, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours after that time. At each time, milk samples were collected manually. Plasma and milk samples were stored at −70°C until analysis by use of HPLC.

Analysis of plasma and milk samples—Ceftazidime concentrations in plasma and milk samples were measured by use of HPLC. The HPLC system included a solvent delivery system, injector, UV absorbance detector (wavelength, 257 nm), and C18 reverse phase column (150 X 4.6 mm; particle size, 5 µm) operating at 30°C; HPLC-grade solvents (water and acetonitrile) and ammonium acetate were used during analysis. The mobile phase was a mixture of 0.02M ammonium acetate buffer (prepared by dissolving 1.534 g of ammonium acetate in 1,000 mL of HPLC-grade water; pH, 4) and acetonitrile (90:10 [vol/vol]), with a flow rate of 1.0 mL/min.

Five hundred microliters of the plasma or milk samples were mixed with 500 µL of acetonitrile and centrifuged for 5 minutes at 3,000 X g. Five milliliters of dichloromethane was added to the upper layer phase, vortexed for 5 minutes, and centrifuged for 5 minutes at 3,000 X g. A volume of 50 µL of supernatant was injected into the HPLC system.

Ceftazidime standard curve—Plasma and milk ceftazidime standard samples (7 ceftazidime concentrations between 0.2 and 100 µg/mL) were prepared with camel plasma and milk samples that did not contain ceftazidime for determination of standard curves. Quality control samples were prepared in large volumes via independent weighing of reference standards, aliquotted into the same type of vials used for storage of plasma and milk samples, and stored at −70°C until analysis. Standard curves were determined by plotting the ceftazidime peak areas versus known concentrations. The standard curve equation was determined by use of the least squares method with linear regression. The standard curve for ceftazidime in camel plasma and milk samples was linear (range of values, 0.2 to 100 µg of ceftazidime/mL). The values of the correlation coefficients (r) were > 0.98.

Validation of the assay method—The precision and accuracy of the HPLC assay were determined with repeated analysis (n = 12 analyses) of the plasma and milk standard samples containing various concentrations of ceftazidime. Percentage recovery of ceftazidime was determined by comparing values of the peak areas of plasma and milk blank samples containing various amounts of drug with the values of the peak areas of samples containing the same amounts of drug prepared in phosphate buffer (n = 6).

Intra-assay variation in data was determined via analysis of 6 replicates of 3 standard samples (0.2, 1, 10, and 20 µg/mL) that were used for determination of standard curves. Despite the high SD relative to the mean value, the intra-assay variation coefficients were 6% and 5% for plasma and milk samples, respectively. Interassay precision of data was determined via analysis of the 3 standard samples on 3 separate days. The interassay variation coefficients were < 7% for plasma samples and < 5% for milk samples. Values for recovery of ceftazidime from plasma and milk samples were 97% and 96%, respectively. The limit of quantitation of the assay for detection of ceftazidime in plasma and milk samples was 0.2 µg/mL.

Pharmacokinetic analysis—A commercially available computer software program was used to analyze the plasma and milk ceftazidime concentration-versus-time curves for each camel. For IV administration of ceftazidime, the appropriate pharmacokinetic model was determined by use of visual examination of each concentration-versus-time curve and the Akaike information criterion. The distribution half-life and elimination half-life were calculated as ln2/α and ln2/β, respectively, where α is the distribution (absorption) rate...
constant and $\beta$ is the elimination rate constant. The volume of distribution during steady-state plasma drug concentration was calculated as the mean residence time $\times$ total body clearance.\textsuperscript{20}

Plasma disposition curves for IM administration of ceftazidime were analyzed by use of the same procedure that was used for analysis of data determined for IV administration of the drug. Each ceftazidime concentration-versus-time curve was analyzed to determine the maximum plasma concentration and the time to maximum plasma concentration. Noncompartmental pharmacokinetic parameters were calculated on the basis of the statistical moment theory.\textsuperscript{19} The terminal elimination half-life and absorption half-life were calculated as $\ln(2)/\beta$ or $\ln(2)/\alpha$, respectively. The area under the plasma concentration-versus-time curve and area under the first moment curve were calculated by use of the method of trapezoids with extrapolation to infinity. The systemic clearance was calculated as the ceftazidime dose divided by the area under the plasma concentration-versus-time curve. The absolute bioavailability was calculated as $\text{AUC}_{\text{IV}}/\text{AUC}_{\text{IM}} \times 100$, where $\text{AUC}_{\text{IV}}$ is the area under the plasma concentration-versus-time curve following IM administration and $\text{AUC}_{\text{IM}}$ is the area under the plasma concentration-versus-time curve following IV administration.

The time-versus-concentration data for milk samples were analyzed on the basis of the ceftazidime concentration in milk samples at each sample collection time. The area under the milk concentration-versus-time curve for ceftazidime was calculated by use of the linear trapezoidal rule with extrapolation to infinity. The amount of distribution of ceftazidime from plasma to milk was expressed as the ratio of the maximum concentration of ceftazidime to the maximum plasma concentration indicated good distribution of ceftazidime to lactating camels in the present study.\textsuperscript{21}

The time that ceftazidime concentration remained $>0.25\, \mu g/mL$ in plasma and milk was calculated with the following formula\textsuperscript{18}:

$$\frac{\ln[B] - \ln[0.25]}{\beta}$$

where $B$ is the intercept of the terminal phase of the pharmacokinetic equation.

**Statistical analysis**—Statistical analysis was performed with commercially available software.\textsuperscript{7} Data were reported as mean $\pm$ SD values. The nonparametric Wilcoxon test was used to compare values of pharmacokinetic parameters for ceftazidime in milk and plasma after IV and IM administration of the drug. Values of $P < 0.05$ were considered significant.

**Results**

No clinical abnormalities of camels were detected during the study. No local signs of pain or soft tissue swelling at injection sites or systemic adverse reactions to ceftazidime were detected in camels after IV or IM administration. Results of the Akaike information criterion test indicated that a 2-compartment open model best represented the plasma concentration-versus-time data following IV or IM administration of ceftazidime to lactating camels.

The mean $\pm$ SD concentrations of ceftazidime in plasma samples collected from camels during each experiment of the study were summarized (Figure 1). The mean $\pm$ SD values of pharmacokinetic parameters estimated by means of curve-fitting analysis for ceftazidime in camels in the present study and pharmacokinetic data for cephalosporins in animals in other studies were summarized (Table 1). Significant differences in plasma elimination half-life, area under the curve, and mean residence time were detected between IV and IM administration of ceftazidime to camels in the present study.

Mean systemic bioavailability of ceftazidime after IM administration was 93.72% (Table 1). Values of pharmacokinetic variables of ceftazidime in milk after IV and IM administration to camels in the present study and the area under the milk concentration-versus-time curve to the area under the plasma concentration-versus-time curve for ceftazidime in plasma or serum of animals in other studies were summarized (Table 2). A 1-compartment open model with first-order absorption best represented the milk concentration-versus-time data following IM administration of ceftazidime to lactating camels in the present study. The values of the ratio of the area under the milk concentration-versus-time curve to the area under the plasma concentration-versus-time curve for ceftazidime and the ratio of the maximum milk concentration of ceftazidime to the maximum plasma concentration of ceftazidime indicated good distribution of ceftazidime from plasma to milk of lactating camels following IV and IM administration. Significant differences in milk elimination half-life, area under the plasma concentration-versus-time curve, and ratio of the area under the milk concentration-versus-time curve to the area under the plasma concentration-versus-time curve for ceftazidime were detected between values for IV and IM administration of the drug.
Table 1—Mean ± SD values of pharmacokinetic parameters for ceftazidime in plasma of 8 female dromedary camels (Camelus dromedarius) in the present study following IV and IM administration of a dose of 10 mg/kg and mean values of pharmacokinetic parameters for various cephalosporin drugs in plasma or serum of animals in other studies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present study</th>
<th>Cefazidime in sheep</th>
<th>Cefazidime in calves</th>
<th>Cefazidime in cows</th>
<th>Cefmani in calves</th>
<th>Ceftriain in calves</th>
<th>Ceftrue in goats</th>
<th>Cefazidime in goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
<td>IM</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Distribution (absorption rate constant (h⁻¹))</td>
<td>2.31 ± 0.41</td>
<td>2.06 ± 0.17</td>
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<tr>
<td>Distribution half-life (h)</td>
<td>0.30 ± 0.02</td>
<td>0.34 ± 0.17</td>
<td>0.22</td>
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<tr>
<td>Elimination rate constant (h⁻¹)</td>
<td>0.25 ± 0.14</td>
<td>0.23 ± 0.01</td>
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<tr>
<td>Elimination half-life (h)</td>
<td>2.85 ± 0.36</td>
<td>3.20 ± 0.28</td>
<td>1.6</td>
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<tr>
<td>Vss (L/kg)</td>
<td>0.21 ± 0.02</td>
<td>ND</td>
<td>0.29</td>
<td>0.48</td>
<td>0.13</td>
<td>0.32</td>
<td>0.1</td>
<td>0.2</td>
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<tr>
<td>Total body clearance (L/kg/h)</td>
<td>0.11 ± 0.01</td>
<td>ND</td>
<td>0.11</td>
<td>0.07</td>
<td>0.03</td>
<td>—</td>
<td>0.04</td>
<td>0.1</td>
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<tr>
<td>AUC (µg·h/mL)</td>
<td>209.74 ± 13.89</td>
<td>195.23 ± 12.89</td>
<td>275.7</td>
<td></td>
<td>261.2 ± 233.3</td>
<td>—</td>
<td>103.4 ± 180.0</td>
<td>165.0 ± 268.4</td>
</tr>
<tr>
<td>Mean residence time (h)</td>
<td>3.96 ± 0.45</td>
<td>4.84 ± 0.37</td>
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<tr>
<td>Cmax (µg/mL)</td>
<td>ND</td>
<td>32.43 ± 2.94</td>
<td></td>
<td>35.7</td>
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<td>67.5</td>
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<tr>
<td>Tmax (h)</td>
<td>20.24 ± 2.74</td>
<td>22.78 ± 2.85</td>
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<tr>
<td>Elimination half-life</td>
<td>0.25 ± 0.41</td>
<td>2.76 ± 0.32</td>
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<tr>
<td>Bioavailability (%)</td>
<td>ND</td>
<td>93.72 ± 18.49</td>
<td></td>
<td>98.9</td>
<td>97.4</td>
<td>93.42</td>
<td>91.7</td>
<td>113</td>
</tr>
</tbody>
</table>

Data for other studies are values after IV administration unless otherwise specified.

*Values for IV and IM administration of ceftazidime to camels in the present study are significantly (P < 0.05) different. †Values for IV and IM administration of ceftazidime to camels in the present study are significantly (P < 0.001) different. ‡Value after IV administration (value after IM administration).

Table 2—Mean ± SD values of pharmacokinetic parameters for ceftazidime in milk of 8 female dromedary camels in the present study following IV and IM administration of a dose of 10 mg/kg and mean values of the area under the milk concentration-versus-time curve to the area under the plasma concentration-versus-time curve for ceftazidime in plasma or serum of animals of other species in other studies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present study</th>
<th>Cows &amp;</th>
<th>Goats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
<td>IM</td>
<td>IV</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>2.35 ± 0.18</td>
<td>2.24 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.71 ± 0.41</td>
<td>2.76 ± 0.32</td>
<td></td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>4.57 ± 1.01</td>
<td>5.14 ± 1.16</td>
<td></td>
</tr>
<tr>
<td>AUC (µg·h/mL)</td>
<td>22.68 ± 3.14</td>
<td>25.03 ± 2.24</td>
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</tr>
<tr>
<td>AUCmilk:AUCplasma</td>
<td>10.81 ± 3.14</td>
<td>12.02 ± 2.13</td>
<td>47.7</td>
</tr>
<tr>
<td>AUCmilk = Area under the milk concentration-versus-time curve. AUCplasma = Area under the plasma concentration-versus-time curve. Cmax = Maximum concentration in milk. Cmax = Maximum concentration in plasma. NA = Data not available. See Table 1 for remainder of key.</td>
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</table>

Discussion

Results of the present study indicated that plasma ceftazidime concentrations decreased in a biexponential manner following IV administration to camels. This finding was similar to findings for ceftazidime administered to calves,10 sheep,10 lactating cows,12 rabbits,9 and lactating goats12; ceftiofur administered to male camels13; and ceftriaxone administered to female camels.16,17 Although results of the present study suggested that IV or IM administration of ceftazidime may have beneficial effects for lactating female camels with mastitis, it is important to acknowledge that this drug is not approved by the US FDA for use in food-producing animals.

Ceftazidime distribution was rapid in camels in the present study following IV administration, as indicated by the finding of a low rate constant, short distribution half-life of 0.30 hours, and elimination half-life of 2.85 hours. Results of other studies indicate lower values of these pharmacokinetic parameters for ceftazidime after IV administration to sheep,10 a lower value of elimination half-life after IV administration to calves,11 and lower values of distribution and elimination half-lives after IV administration to lactating cows.12

Results of the present study indicated a small volume of distribution (0.21 ± 0.02 L/kg) of ceftazidime in lactating camels during steady-state plasma drug concentration. The volume of distribution during steady-state conditions is the variable that indicates the amount of...
a drug in the body as a proportion of the corresponding Cₘ (the expected plasma concentration at steady state). 22 Similar results have been determined for cefetimor16 and ceftriaxone17 in female camels, cefepime in bull calves,15 and ceftriaxone in calves and lactating goats11,14; a higher value of this pharmacokinetic parameter has been determined for cefazidime in lactating cows.12 These volumes of distribution during steady-state conditions are similar to values of that variable for drugs with low distribution to extravascular tissues.23 These differences in results among studies may be attributable to biological differences among species of animals, assay methods used, amount of time between collection of blood samples, or health status and age of animals.

The total body clearance of cefazidime in camels in the present study was 0.11 L/kg/h; this value was consistent with the values determined for cefazidime in calves,11 lactating cows,12 and lactating goats13 and was higher than the values determined for cefepime15 and cefetimor16 in calves. The area under the plasma concentration-versus-time curve determined for cefazidime in camels in the present study was 209.74 µg•h/mL, which was lower than the value determined for that drug in sheep18 and lactating cows12 and higher than the value determined for that drug in lactating goats.14

Following IM administration of cefazidime (10 mg/kg) to camels in the present study, the plasma concentration of cefazidime exceeded the MIC for many susceptible pathogens for a longer time than was found for the drug in cattle after IV administration. The time that the concentration of an antimicrobial drug in plasma remains greater than the MIC is the pharmacodynamic variable that is related to the clinical efficacy of cefazidime. The maximum plasma concentration of cefazidime determined for calves in the present study was 209.74 µg•h/mL, which was similar to the value determined for lactating cows,12 and lower than the value determined for lactating goats.14

The area under the plasma concentration-versus-time curve for cefazidime administered IM to lactating calves in the present study was 195.23 µg•h/mL, which was higher than the value of that variable determined for goats19 and lower than the value determined for lactating cows.12 The elimination half-life of cefazidime after IM administration to calves in this study (mean, 3.20 hours) was significantly longer than the value of that variable after IV administration of that drug (mean, 2.85 hours). This difference in values was likely attributable to continued absorption of cefazidime from the IM injection site during the elimination phase, which would have increased the elimination half-life of the drug.

The systemic bioavailability of cefazidime after IM administration to lactating camels in the present study was calculated to be 93.72%; this value was similar to the value of that variable for cefazidime administered to bull calves,13 cefetimor16 and ceftriaxone17 administered to female calves, and cefazidime administered to lactating cows12; a higher value of that variable was determined for cefazidime administered to lactating goats.14

The systemic bioavailability of cefazidime in camels in the present study suggested that the drug was completely absorbed after IM administration. Differences in results among studies may have been attributable to biological differences among species of animals or to differences in drug formulation used in the studies.

Cefazidime is a weak organic acid, and properties of the liposoluble formulation of the drug (the formulation that allows passage between plasma to milk) are dependent on the dissociation constant of the drug, the pH of the environment, and binding of the drug to proteins in mammary gland tissues and plasma.4 The ratio of the area under milk concentration-versus-time curve to the area under the plasma cefazidime concentration-versus-time curve for cefazidime and the ratio of the maximum milk concentration of cefazidime to the maximum plasma concentration of that drug determined for camels in the present study indicated good distribution of cefazidime from plasma to milk. The values of those ratios determined for camels in this study were lower than the values of those variables determined for cefazidime in milk of lactating goats14 and cows12 in other studies. The lower distribution of cefazidime in milk of calves in this study versus milk of cows in that other study12 may have been attributable to the low milk production of female camels versus that for cows. During mastitis, milk and mammary gland tissues undergo physical and chemical changes that may alter the distribution of drugs. Inflammation of a mammary gland causes changes in vascular permeability and milk composition. Typically, milk pH increases, milk casein concentration decreases, milk albumin concentration increases, concentration of somatic cells in milk increases, and milk fat concentration decreases during mastitis. All of these factors may alter the pharmacokinetic properties of a drug; however, the effects of those factors on drug pharmacokinetics are not well understood.24 Effective systemic treatment of animals with mastitis requires that drugs are easily distributed from circulating blood to milk. Because cefazidime had high systemic bioavailability and good distribution to mammary gland tissues after IM administration to camels in the present study, that drug could be useful in the treatment of camels with severe systemic infections or mastitis, provided microorganisms are susceptible to the drug. However, cefetimor is not detected in milk of female camels after IV or IM administration; therefore, IM administration of cefetimor may not be beneficial for camels with systemic signs of mastitis.16

A long elimination half-life, a low amount of binding to plasma proteins,9,16 and a low molecular weight12 are properties of cefazidime that indicate the drug may have good extravascular distribution; distribution to mammary gland tissue may allow cefazidime to be distributed to milk. The low plasma clearance and slow phase of distribution of cefazidime in camels in this study suggested that the drug may have been distributed to mammary glands.

Results of another study25 indicate that cefazidime has good distribution from treated to untreated mammary gland quarters after intramammary administration to healthy cows and those with mastitis. Drug residues were detected in milk of cows in that study; therefore, milk of cows treated with cefazidime via an intramammary route should be discarded for at least 72 hours after the final treatment. However, results of another study22 indicate that cefazidime residues are detectable for a longer period of time in milk of cows that receive that drug via a parenteral route.

Although MICs of cefazidime for microorganisms isolated from camels have not been determined, to the authors’ knowledge, the Clinical and Laboratory Standards Institute...
has determined a ceftazidime MIC of 32 µg/mL for bacteria of any genus.26 However, the MIC of ceftazidime required to inhibit growth of 90% of Escherichia coli, Salmonella spp, Pasteurella multocida, and Pasteurella haemolytica isolates from calves is 0.01 to 0.25 µg/mL.11 Typically, for cephalosporin antimicrobials, the time during which the circulating drug concentration remains greater than the MIC of an organism is the pharmacokinetic-pharmacodynamic parameter that is most highly correlated with clinical efficacy of the drug.4 However, pharmacokinetic-pharmacodynamic indices predictive of clinical efficacy that are determined by means of in vivo testing are determined on the basis of unbound serum drug concentrations and not on the basis of total serum or tissue drug concentrations, which are important variables for determination of the efficacy of antimicrobial drugs such as ceftazidime.27 Such pharmacokinetic-pharmacodynamic markers should be used with caution for determination of efficacy of cephalosporins because tissue pharmacokinetic properties of such drugs are important for prediction of clinical efficacy. A ceftazidime concentration of 0.25 µg/mL is the limit of quantitation (0.2 µg/mL) of the HPLC assay used to determine drug concentrations in the present study; therefore, such concentrations should be reliably measured. Because plasma concentrations of ceftazidime were 0.25 µg/mL for <24 hours in camels in this study after IV or IM administration, administration of the drug twice per day should cause continuous plasma ceftazidime concentrations of >0.25 µg/mL. That concentration is likely close to the MIC of the drug for pathogenic organisms in camels.

The MICs for ceftazidime against pathogens in camels are unknown, to the authors’ knowledge. Even if such information were available, the ratio of the area under the plasma ceftazidime concentration-versus-time curve at 24 hours after administration to the MIC would not be a good predictor of the clinical efficacy of the drug. Therefore, further studies are warranted to determine pharmacokinetic and pharmacodynamic parameters for prediction of the clinical efficacy of cephalosporins in camels.

On the basis of the pharmacokinetic results of the present study and an assumed ceftazidime MIC of 0.25 µg/mL for most susceptible bacterial pathogens of camels, the drug should be administered twice daily via an IM route to camels to achieve clinically effective plasma concentrations of the drug. Systemic administration of ceftazidime may have beneficial effects on outcomes for female camels with systemic signs attributable to clinical mastitis.

b. Becton Dickinson Vacutainer Systems, East Rutherford, NJ.
c. Solvent delivery system, model 510, Waters Corp, Milford, Mass.
e. Discovery C18 reverse phase column, Supelco, Bellefonte, Pa.
f. Baker Inc, Phillipsburg, NJ.
g. Sigma-Aldrich, St Louis, Mo.
h. R Strip, Micromath Scientific Software, Salt Lake City, Utah.
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