Plasma pharmacokinetics and tissue fluid concentrations of meropenem after intravenous and subcutaneous administration in dogs

Tara Bidgood, DVM, and Mark G. Papich, DVM, MS

Objective—To estimate pharmacokinetic variables and measure tissue fluid concentrations of meropenem after IV and SC administration in dogs.

Animals—6 healthy adult dogs.

Procedure—Dogs were administered a single dose of meropenem (20 mg/kg) IV and SC in a crossover design. To characterize the distribution of meropenem in dogs and to evaluate a unique tissue fluid collection method, an in vivo ultrafiltration device was used to collect interstitial fluid. Plasma, tissue fluid, and urine samples were analyzed by use of high-performance liquid chromatography. Protein binding was determined by use of an ultrafiltration device.

Results—Plasma data were analyzed by compartmental and noncompartmental pharmacokinetic methods. Mean ± SD values for half-life, volume of distribution, and clearance after IV administration for plasma samples were 0.67 ± 0.07 hours, 0.372 ± 0.053 L/kg, and 6.53 ± 1.51 mL/min/kg, respectively, and half-life for tissue fluid samples was 1.15 ± 0.57 hours. Half-life after SC administration was 0.98 ± 0.21 and 1.31 ± 0.54 hours for plasma and tissue fluid, respectively. Protein binding was 11.87%, and bioavailability after SC administration was 84%.

Conclusions and Clinical Relevance—Analysis of our data revealed that tissue fluid and plasma (unbound fraction) concentrations were similar. Because of the kinetic similarity of meropenem in the extravascular and vascular spaces, tissue fluid concentrations can be predicted from plasma concentrations. We concluded that a dosage of 8 mg/kg, SC, every 12 hours would achieve adequate tissue fluid and urine concentrations for susceptible bacteria with a minimum inhibitory concentration of 0.12 µg/mL. (Am J Vet Res 2002;63:1622–1628)

Treatment choices for patients with bacterial infections depend on the cultured or suspected bacteria, location of infection, safety and spectrum of the antimicrobial agent. Because of the increasing emergence of antimicrobial-resistant bacteria, therapeutic choices for managing animals with serious bacterial infections are being driven toward more active antimicrobials to achieve therapeutic success. The choice of antimicrobial for treating an animal with a serious bacterial infection can be limited to expensive and injectable drugs and, occasionally, only a few options are available because of bacterial antimicrobial resistance.

Carbapenems, a new class of β-lactam antimicrobials, offer a promising option for treating many of these infected animals when justified on the basis of microbial culture and results of antimicrobial susceptibility tests. These drugs are advantageous because of their bacterialid and postantibiotic effects that are lacking in other β-lactams. They also are more resistant to most of the β-lactamas, including some of the expanded-spectrum enzymes. Their broad spectrum of activity is a result of efficient penetration into bacteria, stability to β-lactamas, and affinity toward specific penicillin-binding proteins that cause rapid lysis of bacteria. Carbapenems have activity against gram-negative and gram-positive aerobic bacteria, as well as anaerobic bacteria.

Meropenem, the second carbapenem marketed in the United States, offers distinct advantages compared with other drugs. An altered C2 chain is responsible for the increased activity against gram-negative organisms and a low incidence of seizures. Compared to imipenem, meropenem has 2- to 4-fold greater activity against Pseudomonas aeruginosa and a 2- to 32-fold increase in activity against Enterobacteriaceae. Resistance of meropenem has been minimal. Resistance of P. aeruginosa to imipenem has been reported and is primarily attributed to the loss of D2 porin, an important protein for antibiotic penetration; however, meropenem is still 4-fold more active against these isolates.

In a study that examined the susceptibility of P. aeruginosa in vitro, meropenem had the highest percentage of isolates with a minimum inhibitory concentration (MIC) below the breakpoint, compared with imipenem, cefazidime, cefotaxime, piperacillin, gentamicin, amikacin, and ciprofloxacin. Compared to imipenem, meropenem causes minimal nausea and vomiting and is not nephrotoxic or neurotoxic. In a study by Dagan et al., meropenem reached sufficient concentrations in the CSF without causing seizures, and meropenem has been used in human hospitals to treat children with meningitis. Therefore, we anticipate that safe treatment of animals with bacterial infections and concurrent CNS disease by administration of meropenem would be possible.
Meropenem has stability against dehydropeptidase-I (DHPI), a metabolizing enzyme in the renal proximal tubule cells. Therefore, contrary to the situation for imipenem, coadministration of the DHP-I inhibitor, cilastatin, with meropenem is not required.

Intravenous administration of imipenem to dogs requires that the drug be dissolved in large fluid volumes so that the concentration infused is ≤ 5 mg/mL. The increased solubility and stability of meropenem allows it to be administered in a more concentrated solution (50 mg/mL). Injection of a small-volume bolus would be more convenient and advantageous in animals with fluid overload conditions or in the treatment of small or exotic animals. Drugs used for dogs with resistant bacterial infections are usually administered IV. Therefore, treatment of dogs that have refractory infections by the administration of small-volume SC injections would also be a convenient option.

To our knowledge, we are not aware of any pharmacokinetic studies performed with meropenem in dogs to establish guidelines for administration. We also are not aware of any information on the penetration of meropenem or the use of an in vivo ultrafiltration device to determine the relationship between drug concentrations in plasma and tissue fluid. The objective of the study reported here was to obtain plasma pharmacokinetic data that could be used to calculate a dose for administration of meropenem in dogs and, by comparing these values with tissue fluid concentrations of meropenem, to characterize the distribution of meropenem in the body. To obtain an understanding of the distribution of this drug in dogs, an in vivo ultrafiltration device was used to collect interstitial fluid (ISF), and protein-free samples of ISF were then analyzed. Because of the potential for meropenem to be used to treat animals with urinary tract infections caused by resistant bacteria, another objective was to measure the concentration of meropenem in urine after SC administration.

Materials and Methods

Animals—Five adult female Beagles (body weight, 8 to 11 kg) and 1 adult female Collie-crossbred dog (body weight, 20 kg) were used in the study. The dogs were healthy as determined on the basis of results of physical examination and serum biochemical analysis. The study was reviewed and approved by the Institutional Animal Care and Use Committee at North Carolina State University.

Procedure—Dogs were randomly assigned to 2 groups (3 dogs/group). A randomized crossover design was used; thus, each dog received meropenem by each route of administration. Meropenem (50 mg/mL) was prepared in accordance with the manufacturer’s instructions. Dogs were given meropenem (20 mg/kg) as a single IV injection through a catheter inserted into the cephalic vein or as a single SC injection in the dorsal lumbar region. There was a 7-day washout period between treatments. Hair was clipped over the site of the SC injection to allow us to monitor signs of a localized injection reaction.

Collection of blood samples—A catheter was placed into the jugular vein of each dog 18 hours before the start of the experiment, and a catheter was placed in the cephalic vein of those dogs that were receiving meropenem via IV administration immediately before the start of the experiment. Blood samples were collected from the jugular vein into evacuated glass tubes that contained sodium heparin as the anticoagulant. Samples were collected immediately before administration (time 0) and 10, 20, and 40 minutes and 1, 2, 4, 6, 8, 12, 16, and 24 hours after administration. Blood samples were centrifuged at 1,000×g for 10 minutes. Plasma was then harvested and stored at –70°C until analysis.

Collection of urine samples—Urine was collected from each dog 3 times after SC administration of meropenem (between 6 and 8 hours after administration, between 8 and 12 hours after administration, and between 12 and 24 hours after administration). Urine samples were obtained by mid-stream catch or cystocentesis. Aliquots (3 mL) were stored at –70°C until analysis.

Collection of tissue fluid—Tissue fluid was collected from SC tissues by use of an in vivo ultrafiltration sampling kit. The ultrafiltration probe contained 3 loops, each consisting of a semipermeable membrane that was 12 cm in length. The 3 loops connected to a nonpermeable tube. The membrane in the loop consisted of pores that allowed water, electrolytes, and low-molecular-weight molecules (< 30 kd) to pass. Therefore, the fluid collected was free of protein and other large-molecular-weight compounds.

A bleb of lidocaine was injected SC, and the ultrafiltration probe was inserted into the SC tissues of each dog by use of a guide needle. Once the probe was in place, the guide needle was removed. The semipermeable portion of the probe remained under the skin in the interstitial space, and the nonpermeable tube exited the skin of the dog and was attached to a 3-mL evacuated glass tube for collection of samples. The evacuated tube provided negative pressure for fluid collection. A new probe was inserted at another site, because it was necessary to combine fluid from the 2 probes to provide a sufficient volume of tissue fluid for analysis. Probes were removed immediately after collection of the final sample for each route of administration.

The ultrafiltration probes were inserted into the SC tissues 18 hours prior to the start of the experiment to allow fluid in the tissue space and the tube to reach equilibrium. Interstitial fluid was collected at time 0 and 1, 2, 4, 6, 8, 12, 16, and 24 hours after IV and SC administration. The fluid was immediately frozen at –70°C until analysis.

Analysis of meropenem concentrations—Plasma, tissue fluid, and urine samples were analyzed by reverse-phase high-performance liquid chromatography (HPLC) to determine concentrations of meropenem. Separation was achieved at 40°C by use of a C18, 4.6 × 150-mm reverse-phase column. This system included 2 pumps, a pump controller, an automated sampler, and a UV light detector. Solid-phase extraction was performed initially for plasma and urine samples (diluted 1:10 [vol:vol] with distilled water), followed by reverse-phase chromatography with UV detection at 296 nm. Samples of tissue fluid were analyzed directly by HPLC without extraction. The mobile phase consisted of 85% 0.01M acetic buffer and 15% methanol (pH 4.3) at a flow rate of 1 mL/min. Retention time for meropenem was between 4.4 and 4.6 minutes for plasma, between 4.4 and 4.9 minutes for tissue fluid, and between 4.7 and 4.8 minutes for urine. Calibration curves in the range of 0.1 to 100 μg/mL were prepared by use of pooled canine plasma, pooled canine urine, and PBS solution (pH 7.38) prior to analyzing each set of plasma, urine, or tissue fluid samples, respectively. Minimum acceptable value for r² was 0.99. The assay was validated by use of a pure reference standard. Calibration curves and validation tests were all within 15% of the true concentration of meropenem.

Protein binding—Protein binding studies of plasma
samples were performed by use of a micropartition device. Four replicates of identical concentration were prepared by spiking pooled canine plasma with a stock solution of meropenem prepared from the pure reference standard. The replicates were incubated in a water bath (37°C for 30 minutes). One milliliter from each replicate was placed into the reservoir of each of 4 micropartition devices. The devices were centrifuged (1,500 × g for 30 minutes). Approximately 300 µL of ultrafiltrate was collected in the filtrate cup. Solid-phase extraction of the ultrafiltrate as described previously was performed prior to analysis by use of HPLC. The resulting concentrations represented the total (bound and unbound) fraction. The standard curve used to determine protein concentrations was prepared by use of 300 µL of spiked pooled canine plasma. Percentage of the bound fraction was calculated by use of the following equation:

\[
\text{percentage of protein binding} = \left(1 - \frac{\text{total concentration} - \text{unbound concentration}}{\text{total concentration}}\right) \times 100
\]

Pharmacokinetic analysis—Pharmacokinetic variables after IV administration were estimated by use of a computer software program. Data for IV administration were plotted with a weighting factor of 1/\(Y^2\), where Y is the predicted plasma concentration of meropenem. The model that provided the best fit for the data was determined by applying Aikake information criterion. Concentrations in tissue fluid were analyzed by use of noncompartmental modeling. Values for total body clearance, elimination half-life (\(t_{1/2}\)), mean residence time (MRT), and volume of distribution of the area during the elimination phase (\(V_{d\text{ss}}\)) were estimated by use of noncompartmental methods. The \(AUC_{0-\text{\infty}}\) was estimated by use of the log-linear trapezoidal rule and extrapolated to infinity by use of the following equation:

\[
AUC_{0-\infty} = \frac{C}{\lambda_z}
\]

where \(C\) is the concentration for the last time point and \(\lambda_z\) is the first-order rate constant associated with the terminal portion of the curve. Systemic availability (bioavailability [F]) was calculated by use of the following equation:

\[
F = \frac{AUC_{\text{ss}}}{AUC_{\text{IV}}}
\]

where \(AUC_{\text{ss}}\) is the area under the curve (AUC) calculated after SC administration and \(AUC_{\text{IV}}\) is the AUC after IV administration. The MRT was calculated by use of the statistical moment theory as follows:

\[
\text{MRT} = \frac{AUMC_{0-\text{\infty}}}{AUC_{0-\text{\infty}}}
\]

where \(AUMC_{0-\text{\infty}}\) is the area under the moment curve. Half-life was calculated using the formula

\[
\text{t}_{1/2} = 0.693/\lambda_z
\]

Distribution \(t_{1/2}\), elimination \(t_{1/2}\), micorrate constants, intercepts, and rate constants were calculated from equations published elsewhere. Micorrate constants and intercepts were calculated for a 2-compartment model and averaged for 5 dogs.

Stability during storage—Stability of meropenem during refrigeration storage was evaluated. A solution (concentration of 10 µg/mL) was prepared and stored at 7°C for 53 days. Aliquots of the solution were obtained at 2-day intervals and analyzed for meropenem concentration.

Determination of meropenem dosing regimens—A computer simulation was used to determine meropenem dosing regimens for organisms commonly found in dogs and often associated with antimicrobial resistance. Pharmacokinetic variables estimated in the study reported here for the 2-compartmental (IV) and 1-compartmental (SC) analysis were used for the simulation. Three dosing regimens were analyzed for Enterobacteriaceae (24 mg/kg, IV, q 12 h; 3 mg/kg, IV, q 8 h; 8 mg/kg, SC, q 12 h), and 2 dosing regimens were analyzed for other organisms (24 mg/kg, IV, q 8 h and 12 mg/kg, SC, q 8 h). For these simulations, the MIC of meropenem for Enterobacteriaceae (0.12 µg/mL) and other organisms (1 µg/mL) were based on reports of numerous isolates from humans because of the lack of MIC information for meropenem in bacteria isolated from dogs.

Statistical analysis—Mixed-effects models with differing correlation structures were used to analyze the data. The most appropriate model was selected on the basis of Aikake information criteria and Schwarz’s Bayesian Criterion. A mixed model with 1-dependent correlation structure was selected. Also, estimated pharmacokinetic variables (\(\lambda_z\), \(t_{1/2}\), and \(AUC_{0-\text{\infty}}\)) were compared between routes of administration (IV and SC) for plasma and tissue fluid on the basis of an ANOVA conducted on logarithmically transformed data. Values of \(P \leq 0.05\) were considered significant.

Results

We did not detect adverse effects in any of the dogs after IV or SC administration of meropenem. The SC injections did not appear to elicit a painful reaction, the site of injections were not swollen or hot, and we did not elicit signs of pain when they were examined at intervals coinciding with times of blood collection.

Plasma concentrations of meropenem after IV administration best fit a 2-compartment model for 5 of 6 dogs and a 1-compartmental model for the remaining dog. A 1-compartmental model with first-order input fit plasma concentrations of meropenem after SC administration in all dogs. Correlations were found among concentrations determined over time within dogs. Statistical results based on this model revealed that there were significant \((P < 0.001)\) time-dependent effects for plasma and tissue fluid concentrations of meropenem after IV and SC administration. On the basis of the results of the correlation test, there was a significant \((P \leq 0.007)\) strong positive correlation between concentrations in tissue fluid and plasma for IV and SC administration (Table 1).

The limit of quantification (LOQ) and limit of detection (LOD) after IV administration were 0.016 and \(< 0.01\) µg/mL, respectively, for plasma and 0.366 and 0.106 µg/mL, respectively, for tissue fluid. The LOQ and LOD after SC administration were 0.019 and \(< 0.01\) µg/mL, respectively, for plasma and 0.43 and 0.126 µg/mL, respectively, for tissue fluid. These values are lower for plasma after both routes of administration, because plasma was concentrated 5-fold during the process of extraction and reconstitution as compared with tissue fluid, which was analyzed directly without extraction.

Stability of meropenem during refrigeration storage was evaluated. Concentrations remained within 90% of the original concentration (between 9 and 10 µg/mL) for 23 days. On day 41, the concentration measured was 7.50 µg/mL; however, by day 53, the...
concentration had decreased to 0.56 µL/mL. The acceptable concentration range for the meropenem injectable product is reportedly between 90 and 120% of the true concentration.

Table 1—Mean ± SD values for pharmacokinetic variables of meropenem after IV and SC administration (20 mg/kg) to 6 healthy adult dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma</th>
<th>Tissue fluid</th>
<th>Plasma</th>
<th>Tissue fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cmax (µg/mL)</strong></td>
<td>NA</td>
<td>24.32 ± 8.93</td>
<td>24.56 ± 6.12</td>
<td>10.95 ± 0.99</td>
</tr>
<tr>
<td><strong>AUC0-infinity (h • µg/mL)</strong></td>
<td>53.29 ± 12.04</td>
<td>73.71 ± 14.56</td>
<td>63.42 ± 14.24</td>
<td>43.22 ± 14.39</td>
</tr>
<tr>
<td><strong>AUMC0-infinity (h • h • µg/mL)</strong></td>
<td>47.76 ± 16.31</td>
<td>183.64 ± 67.98</td>
<td>138.25 ± 52.83</td>
<td>199.26 ± 95.78</td>
</tr>
<tr>
<td><strong>ClT (mL/min/kg)</strong></td>
<td>6.53 ± 1.51</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Vdss (L/kg)</strong></td>
<td>0.372 ± 0.053</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Vdarea (L/kg)</strong></td>
<td>2.08 ± 0.08</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Tmax (h)</strong></td>
<td>NA</td>
<td>2</td>
<td>0.67 ± 0.05</td>
<td>3.67 ± 1.15</td>
</tr>
<tr>
<td><strong>λz (h)</strong></td>
<td>1.05 ± 0.11</td>
<td>0.70 ± 0.26</td>
<td>0.74 ± 0.17</td>
<td>0.587 ± 0.17</td>
</tr>
<tr>
<td><strong>t1/2α (h)</strong></td>
<td>0.08 ± 0.05</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>t1/2β (h)</strong></td>
<td>0.69 ± 0.08</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>K01 t1/2 (h)</strong></td>
<td>NA</td>
<td>2.44 ± 0.42</td>
<td>2.14 ± 0.28</td>
<td>4.48 ± 0.79</td>
</tr>
<tr>
<td><strong>K10 t1/2 (h)</strong></td>
<td>0.88 ± 0.13</td>
<td>NA</td>
<td>NA</td>
<td>84.037</td>
</tr>
<tr>
<td><strong>K12 (h)</strong></td>
<td>4.54 ± 3.94</td>
<td>NA</td>
<td>0.88 ± 0.23</td>
<td>NA</td>
</tr>
<tr>
<td><strong>K21 (h)</strong></td>
<td>5.31 ± 4.51</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>K01 (h)</strong></td>
<td>3.12 ± 0.57</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>A (µg/mL)</strong></td>
<td>218.64 ± 223.45</td>
<td>NA</td>
<td>1.22 ± 0.52</td>
<td>NA</td>
</tr>
<tr>
<td><strong>B (µg/mL)</strong></td>
<td>46.50 ± 8.14</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>α (h)</strong></td>
<td>11.94 ± 8.02</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>β (h)</strong></td>
<td>1.03 ± 0.13</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Protein binding (%)</strong></td>
<td>11.87</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Calculated by use of a 2-compartment model and averaged from 5 dogs.

Cmax = Maximum concentration. AUC0-infinity = Area under the curve from time 0 to infinity. AUMC0-infinity = Area under the first moment curve from time 0 to infinity. ClT = Total body clearance. Vdss = Volume of distribution at steady state. Vdarea = Volume of distribution of the area during the elimination phase. Tmax = Time until maximum concentration. λz = First-order rate constant of terminal portion of the curve. λz t1/2 = Half-life of the terminal portion of the curve. t1/2α = Distribution half-life. t1/2β = Elimination half-life. K01 t1/2 = Half-life of absorption phase. K10 t1/2 = Half-life of elimination phase. MRT = Mean residence time. F = Bioavailability. K10 = Elimination rate from compartment 1. K12 = Rate of movement from compartment 1 to compartment 2. K21 = Rate of movement from compartment 2 to compartment 1. K01 = Absorption rate. A = Intercept for elimination phase. B = Intercept for distribution phase. α = Rate constant associated with distribution phase. β = Rate constant associated with elimination phase. NA = Not applicable for the route of administration.

Plasma (total and free) and tissue fluid concentrations of meropenem after IV and SC administration were plotted against time on a semilogarithmic graph (Fig 1 and 2). Values above the LOD were detected, but only values above the LOQ were used in the pharmacokinetic analysis. At 8 hours after IV administration, 2 values for plasma were above the LOQ, but when averaged for all 6 dogs, the mean value was below the LOQ. Tissue fluid was not collected in 2 dogs until 2
Discussion

Resulted in meropenem concentrations above the respective antimicrobial agents. Results from the IV and SC experiments reported here provide pharmacokinetic information to guide dosing regimens for either route of administration and to help clinicians and researchers understand the disposition of meropenem in dogs.

Meropenem was consistently detectable in the urine of all dogs at 8 hours but not 12 hours after administration. Mean concentration at 8 hours was 1,296 µg/mL (range, 565 to 2,150 µg/mL). This was substantially higher than the mean plasma concentration at 8 hours (0.37 µg/mL; range, 0.1 to 1.39 µg/mL).

Results of the computer simulation for meropenem dosing regimens for organisms commonly found in dogs and often associated with antimicrobial resistance were analyzed. All dosing regimens used in the simulation resulted in meropenem concentrations above the respective MIC for longer than half of the dosing interval.

Concentrations and pharmacokinetic variables reported here were determined in healthy dogs. In a recent study43 in which investigators evaluated concentrations after coadministration of probenecid.16,37,41 Urine samples were collected once during each of 3 intervals after SC administration. The samples obtained from all dogs during the interval between 6 and 8 hours had concentrations > 1 µg/mL. These results also indicated that a DHP-1 inhibitor, such as cilastatin, is not required to prevent hydrolysis in dogs, which is contrary to the situation for imipenem.

Concentrations of meropenem in tissue fluid and plasma were strongly correlated (P < 0.001). This can be explained by the rapid distribution of meropenem to the interstitial space. Geometry of a compartment is described by the ratio of surface area to volume, and this determines the rate and extent of equilibrium established.2 With a larger ratio for surface area to volume, a greater correlation between plasma and tissue fluid should be expected.2 The interstitial space is considered a compartment with a large surface area-to-volume ratio. After correcting for the lag time for collection of tissue fluid, analysis revealed that tissue fluid had similar peak concentrations, time to peak concentration, and t1/2, compared with values for plasma (Fig 1 and 2). Although protein binding (11.87%) in the dogs of our report was higher that that reported for humans (2%), the value is considered low when compared with values for highly bound drugs. Pharmacokinetic characteristics of meropenem include a short t1/2, high clearance, and low volume of distribution. Based on these characteristics, this drug would be expected to reach equilibrium quickly between tissue and plasma, and concentrations in tissue fluid (ie, ISF) should resemble concentrations in unbound plasma. The results from the study reported here confirm these assumptions, and this information can be used to predict ISF concentrations of other drugs with similar pharmacokinetic and physiochemical properties.

There was a significant (P = 0.002) difference in t1/2 between IV and SC routes for plasma, but there was not a significant (P = 0.852) difference for t1/2 between IV and SC routes for tissue fluid. Mean drug concentrations after IV administration remained > 1 µg/mL for more than 6 hours in tissue fluid and slightly less than 4 hours in plasma.

Meropenem is eliminated by metabolism and excretion, with up to 79% of the administered dose eliminated unchanged in the urine in humans and the rest excreted as an inactive metabolite.2,35 Mean clearance (6.53 ± 1.51 mL/min/kg) reported here was higher than the glomerular filtration rate reported for dogs in another study (4 mL/min/kg).2 This can be explained by tubular secretion in addition to glomerular filtration being responsible for elimination of the drug, which is typical for β-lactams. These findings are consistent with reports2,24,32,36 in humans and are supported by the reduction of renal clearance equivalent to glomerular filtration after coadministration of probenecid.24,25 Urine samples were collected once during each of 3 intervals after SC administration. The samples obtained from all dogs during the interval between 6 and 8 hours had concentrations > 1 µg/mL. These results also indicated that a DHP-1 inhibitor, such as cilastatin, is not required to prevent hydrolysis in dogs, which is contrary to the situation for imipenem.

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Concentrations and pharmacokinetic variables reported here were determined in healthy dogs. In a study2 in which investigators evaluated concentrations in plasma and tissue fluid (via microdialysis) in healthy and seriously ill human patients, there was little difference in plasma concentrations or plasma AUC values between the 2 groups. However, when drug concentrations in tissue fluid and diffusion rate constants...
were compared, seriously ill patients had a significantly lower drug concentration in tissue fluid and slower rate of tissue distribution than did healthy patients. Because concentrations in tissues of seriously ill human patients were less than the targeted MIC for most of the dosing interval, the author of that study suggested that making dosage adjustments on the basis of drug concentrations in plasma may be misleading. Additional studies are necessary to evaluate the effect of disease on tissue distribution and pharmacokinetic variables in dogs. Our study reported here provides a method whereby this could be examined.

The ultrafiltration probes were easily implanted, and HPLC analysis of tissue fluid did not require an extraction step. Analysis of results reported in this study indicates that ultrafiltration is a reliable, easy, and useful method for the evaluation of drug disposition in dogs. It could potentially replace surgical collection of tissue samples, which often requires euthanizing animals to enable investigators to obtain tissue samples, or the use of tissue cages for estimating concentrations in tissues. Moreover, we believe that this method of sample collection of ISF is more representative of drug concentrations needed to counteract bacterial infections, compared with results obtained by use of whole-tissue homogenates or artificial tissue cages.

To make use of pharmacokinetic variables, correlation with in vitro MIC pharmacodynamic variables can be used to derive optimum dosages. The β-lactam antimicrobials kill bacteria in a time-dependent fashion; therefore, the amount of time for which concentrations are greater than the MIC is the most important factor when considering a dosing regimen. Some recommendations have suggested administering β-lactam antimicrobials as a continuous infusion to achieve this goal. Carbapenem antimicrobials differ from other β-lactams, because they have a postantibiotic effect for gram-negative and gram-positive bacteria (ie, there is continued inhibition of bacterial growth after the drug concentration decreases to less than the MIC). Duration of the postantibiotic effect depends on the dose, duration of antibiotic exposure, and organism. The required amount of time that concentrations need to be above the MIC for efficacy is lower for carbapenems (33% to 40%), compared with other β-lactam antimicrobials (50% to 60%). In addition, bacterial MICs for meropenem are lower than for other β-lactams, which allows use of lower doses and intermittent dosing of these antimicrobials.

In a report by the National Committee for Clinical Laboratory Standards, break points for imipenem and meropenem in humans were ≤ 4 µg/mL (susceptible), 8 µg/mL (intermediate), and ≥ 16 µg/mL (resistant). However, published MIC values are often much lower. In a study in which investigators project the plasma concentration-versus-time curve onto the MICs for Streptococcus pyogenes, Neisseria meningitides, S pneumoniae, N gonorrhoeae, Shigella spp, Salmonella spp, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, Listeria monocytogenes, Enterobacter cloacae, and Bacteroides fragilis, it was revealed that meropenem administered to children at a dosage of 20 mg/kg every 8 or 12 hours was sufficient for all organisms. In that same study, patients with infections attributable to P aeruginosa were effectively treated by use of dosing at 8-hour intervals.

Escherichia coli, Klebsiella spp, and Staphylococcus spp are the bacteria most commonly cultured from canine urine. Antimicrobial resistance to these and other organisms can pose a therapeutic challenge. Two important therapeutic uses of meropenem would be for treating infections caused by bacteria resistant to other antimicrobials and to replace the use of multiple antimicrobials for animals with mixed infections. This would potentially decrease duration of hospitalization, reduce the use of other drugs to which resistance may develop (eg, fluoroquinolones), and decrease the use of potentially toxic drugs (eg, aminoglycosides).

We documented that meropenem has excellent penetration of tissue fluid, good concentrations in urine, low protein binding, and is easy to administer without adverse effects. Because meropenem is eliminated through the renal system and has a postantibiotic effect, the amount of time that concentrations need to be greater than the MIC is only 33 to 40% of the dosing interval; infections of soft tissues or the urinary tract that are attributable to bacteria that have a MIC of 0.12 µg/mL could be treated with dosages as low as 8 mg/kg, SC, every 12 hours. More resistant infections caused by organisms such as Pseudomonas spp with a MIC of 1.0 µg/mL may require higher dosages of 12 mg/kg, SC, every 8 hours.

References


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