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Pharmacokinetics of meropenem after intravenous, intramuscular and subcutaneous administration to cats

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Abstract

Objectives The aim of the study was to describe the pharmacokinetics and predicted efficacy of meropenem after intravenous (IV), intramuscular (IM) and subcutaneous (SC) administration to cats at a single dose of 10 mg/kg.

Methods Five adult healthy cats were used. Blood samples were withdrawn at predetermined times over a 12 h period. Meropenem concentrations were determined by microbiological assay. Pharmacokinetic analyses were performed with computer software. Initial estimates were determined using the residual method and refitted by non-linear regression. The time that plasma concentrations were greater than the minimum inhibitory concentration (T >MIC) was estimated by applying bibliographic MIC values and meropenem MIC breakpoint.

Results Maximum plasma concentrations of meropenem were 101.02 µg/ml ($C_{p(0)}$, IV), 27.21 µg/ml (C_{max}, IM) and 15.57 µg/ml (C_{max}, SC). Bioavailability was 99.69% (IM) and 96.52 % (SC). Elimination half-lives for the IV, IM and SC administration were 1.35, 2.10 and 2.26 h, respectively.

Conclusions and relevance Meropenem, when administered to cats at a dose of 10 mg/kg every 12 h, is effective against bacteria with MIC values of 6 µg/ml, 7 µg/ml and 10 µg/ml for IV, IM and SC administration, respectively. However, clinical trials are necessary to confirm clinical efficacy of the proposed dosage regimen.

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Introduction

Meropenem is a β-lactam antibiotic of the carbapenem class with a wide spectrum of activity that includes most pathogenic bacteria. It is highly active against many aerobic and anaerobic gram-positive (except methicillin-resistant strains of *Staphylococcus* and *Enterococcus* species) and gram-negative bacteria (*Enterobacteriaceae* species and *Pseudomonas aeruginosa*, including extended-spectrum β-lactamases [ESBL]-producing strains) and it is relatively stable against the hydrolysis of many β-lactamases. Carbapenems are more potent bactericidal and have longer post-antibiotic effect than other β-lactams because they bind to PBP-1 and PBP-2.[1] Susceptibility breakpoint for human isolates is ⩽0.5 µg/ml for *Streptococcus* species β-hemolytic group, ⩽1 µg/ml for *Enterobacteriaceae* and ⩽2 µg/ml for *Pseudomonas aeruginosa*;[2] however, many bacteria isolated from humans exhibit a lower minimum inhibitory concentration (MIC; ⩽0.125 µg/ml)[3] than MIC breakpoint.

β-Lactam antibiotics kill bacteria in a time-dependent manner; therefore, the time that plasma concentrations are greater than the MIC (T >MIC) is the best efficacy predictor.[4] As carbapenems have greater bactericidal activity and longer post-antibiotic effects than other β-lactams, the T >MIC may be as low as 20–40% (for bacteriostatic or bactericidal effects) of the dose interval.[5,6] However, a greater T >MIC is indicated to decrease the risk of the development of resistance.[7]

Meropenem differs from imipenem in some characteristics. It is more active against gram-negative rods, especially *P aeruginosa*, it does not require cilastatin co-administration because is stable to renal

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dihydropeptidase-1, and because of this has a prolonged terminal half-life and lacks of the potentially nephrotoxic effect of imipenem metabolites.[8]

The pharmacokinetics of meropenem have been studied in dogs after intravenous (IV) and subcutaneous (SC) administration,[9] and ewes after IV and intramuscular (IM) administration.[10] It has a wide distribution into extravascular fluid and rapid elimination, mainly unchanged, through the kidney.

The clinical use of carbapenems in human and veterinary medicine is reserved for severe infections refractory to more common antibiotics (ie, infections caused by cephalosporin-resistant members of the family Enterobacteriaceae and some anaerobes, and for empirical treatment of febrile illness in neutropenic patients).[8,11] Therefore, in order to minimize the emergence of microbial resistance and ensure the eradication of bacteria, it is essential to have dosage regimens based on pharmacokinetic data and pharmacokinetic/pharmacodynamic integration.

Pharmacokinetic studies of meropenem in domestic animals are very scarce. It has been described only in dogs and ewes.[9,10,12] To our knowledge, there have not been any reports in cats. The objective of the present study was to describe the pharmacokinetics of meropenem and to predict efficacy based upon pharmacokinetic data of meropenem after IV, IM and SC administration to cats after single doses of 10 mg/kg.

Materials and methods

Animals

Five adult mixed-breed cats (two females, three males) weighing 4.75 ± 0.53 kg were used. Animals were healthy as determined by clinical examination, complete blood and serum biochemical analysis and urinalysis. Cats were housed at the Faculty of Veterinary Medicine, University of Buenos Aires, and allowed to acclimatize for 2 months before the experiments. Access to high-quality dry food (Purina ProPlan) and water was ad libitum.

The study protocol was approved by the Institutional Animal Care and Use Committee, University of Buenos Aires, Argentina.

Dosage forms

A commercially available formulation of meropenem (Merozen; AstraZeneca) was used. Before administration, the powder was dissolved in sterile saline solution (0.9% NaCl), according to the manufacturer's instructions, to a concentration of 50 mg/ml. Meropenem was administered IV, IM and SC at a dose of 10 mg/kg.

Experimental design

A three-period, three-treatment crossover design was used. As a result, each animal received meropenen IV, IM and SC in a randomized sequence. Before the studies and, for placement of IV catheters and to facilitate animal handling, cats were sedated with romifidine 0.15 mg/kg IM (Romidys; Virbac) and tramadol 1 mg/kg IM (Algen20; Richmond Vet Pharma).

For meropenem IV administration, the dose was given via bolus (over a 1 min period) through a catheter placed in the cephalic vein. For the IM route, the dose was administered in the dorsal lumbar muscles, and for the SC administration, the dose was injected into the loose skin over the shoulders. Two-week intervals were allowed between each period.

Sampling procedures

Blood samples (0.7 ml) were collected via a catheter placed in the cephalic vein prior to drug administration and at 0.083, 0.16, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h. Samples were taken with heparinized syringes, placed into tubes, mixed and kept on ice until plasma separation. Plasma was separated after centrifugation (15 mins at 1500 × *g*) and stored at 4ºC and analyzed within 6 h of collection.

Plasma drug analysis

Plasma concentrations of meropenem were determined by microbiological assay using *Bacillus subtilis* ATCC 6633 as the test microorganism.[13] Standard curves were prepared in normal cat plasma on the day of each study. The assay was linear from 0.19 to 100.00 µg/ml, with inter- and intra-assay variation of <10%. The lower limit of detection and quantification (LLOQ) of the method were 0.19 µg/ml and 0.39 µg/ml, respectively. The LLOQ was the lower limit of concentration used in the pharmacokinetics analysis.

Pharmacokinetic analysis:

Pharmacokinetic analyses were performed with computer software (Phoenix WinNonlin 6.3, 2005–2012; Certara, LP). Initial estimates were determined using the residual method and refitted by non-linear regression.[14]

The number of exponents needed for IV, IM and SC administration data were determined by applying the Akaike information criterion and the residual distribution around the estimated concentrations.[15]

Pharmacokinetic parameters (area under the curve from time 0 to infinity [$AUC_{(0-\infty)}$], distribution half-life [$t_{½(d)}$], elimination half-life [$t_{½}$], absorption half-life [$t_{½(a)}$], microrate constants [λ_1, λ_2], intercepts [C_1 C_2], rate constants [K_{12},K_{21}, K_a], volume of distribution of the area during the elimination phase [V_{area}], volume of distribution at the steady state [$V_{(d(ss))}$], maximum plasma concentration [C_{max}], time of maximum plasma concentration [T_{max}], total body clearance [Cl_B]), were calculated using classic equations associated with compartmental

analysis.[14] Bioavailability (F) was calculated by the following equation:

$$F = (AUC_{\text{extravascular administration}} / AUC_{\text{intravascular administration}}) \times 100$$

Also, the extent of meropenem protein binding in plasma of cats was determined by using the method described by Craig and Suh,[16] based on the diffusion of free antibiotic into the agar medium.

Statistical analysis

All data are presented as mean and SD. Main estimated pharmacokinetic parameters were statistically compared for the different administration routes, applying an ANOVA test ($AUC_{(0-\infty)}$, $t_{½}$) or a *t*-test (K_a, $t_{½(a)}$, T_{max}, C_{max}, F) (GraphPad Prism Version 5.00). Results were considered significant when $P \leqslant 0.05$.

PK/PD integration

Time above the MIC (T>MIC) for the three different administration routes was estimated by visual approximation from the plasma concentration vs time curve.

The MIC, as well as break-point values considered for T>MIC estimation ($MIC_{90} = 0.125$ µg/ml for Enterobacteriaceae ESBL non-producing strains (ESBL–) and producing strains (ESBL+) groups,[17] and penems Clinical and Laboratory Standards Institute break point (MIC ⩽1 µg/ml),[2] were obtained from human reports as, so far, there are no values reported for bacteria isolated from cats.

Results

No adverse effects during or after meropenem administration were recorded by physical examination in any of the cats.

Mean ± SD meropenem concentrations vs time curves after IV, IM and SC administration to five cats are shown in Figure 1 and estimated pharmacokinetic parameters in Table 1.

Meropenem plasma concentrations after intravascular administration were best described as a two-compartment model. Disposition curves obtained after extravascular administrations were best described as a one-compartment model with first-order input.

Meropenem showed a rapid, though quite variable, distribution, as reflected by the rate constant of the process (λ_1 11.19 ± 10.71 h^{-1}) and its short distribution half-life ($t_{½(d)}$ 0.35 ± 0.57 h) after IV administration. The extent of distribution was moderate and typical for a β-lactam, with a volume of distribution ($V_{(d(ss))}$) of 0.21 ± 0.05 l/kg.

Meropenem elimination was rapid as reflected by a clearance (Cl_B) of 0.11 ±0.01 l/h/kg and an elimination half-life ($t_{½}$) of 1.35 ± 0.25 h after IV administration.

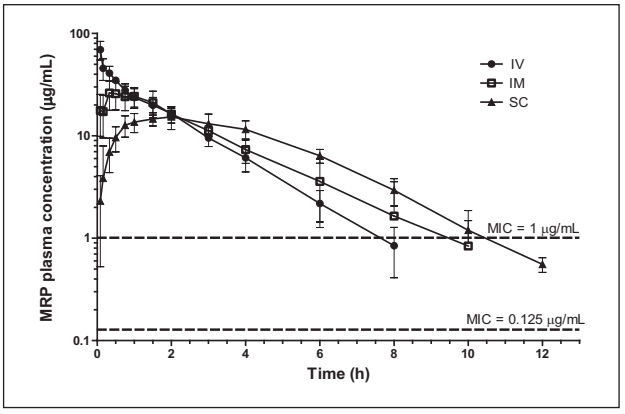

Figure 1 Meropenem (MRP) plasma concentration–time profile (mean ± SD) after intravenous (IV) (●), intramuscular (IM) (■) and subcutaneous (SC) (▲) administration at a dose of 10 mg/kg to cats (n = 5)

For extravascular routes, meropenem absorption was faster after IM than SC administration; statistically significant differences between both routes were observed in parameters associated with this process, such as K_a, $t_{½(a)}$, T_{max} and C_{max}. However, the extent of the absorption was the same for both routes, with a bioavailability of 99.69 ± 18.57% and 96.52 ± 8.42% for IM and SC administration, respectively.

Plasma protein binding of meropenem in cats was low, in the range of 1.54–9.38% for concentrations of 50 µg/ml and 0.39 µg/ml, respectively.

As shown in Figure 1, concentrations above the MIC for highly susceptible microorganisms (⩽0.125 µg/ml) were maintained up to the last sampling time on the three administration routes. For less susceptible bacteria (MIC breakpoint, MIC ⩽1 µg/ml), T >MIC was around 6 h, 8 h and 10 h for the IV, IM and SC routes, respectively.

Discussion

Carbapenems are appropriate empirical choices when resistant bacteria are suspected. However, their use should be restricted to infections that cannot be treated with other antibiotics of first or second choice.

Correct use of this antimicrobial group requires knowledge of both the effects on the pathogens causing the infection and the pharmacokinetic properties of the antimicrobials.

Therefore, the results presented in this study will be useful in optimizing the therapeutic use of meropenem in cats.

Generally, the meropenem pharmacokinetic profile after IV administration was as expected for a β-lactam and was similar to that reported in dogs, ewes and humans,[3,9,10] characterized by a fast distribution into the extracellular fluid and relatively rapid renal excretion.

Table 1 Pharmacokinetic parameters (mean ± SD) of meropenem after intravenous (IV), intramuscular (IM) and subcutaneous (SC) administration at single doses of 10 mg/kg to cats (n = 5) in a crossover design

Pharmacokinetic parameter	IV administration (mean ± SD)	IM administration (mean ± SD)	SC administration (mean ± SD)
C_1 (μg/ml)	56.06 ± 52.70	–	–
C_2 (μg/ml)	44.96 ± 9.74	–	–
$C_{p(0)}$ (μg/ml)	101.02 ± 61.61	–	–
λ_1 (h^{-1})	11.19 ± 10.71	–	–
λ_2 (h^{-1})	0.53 ± 0.09	–	–
$AUC_{(0-\infty)}$ (μg/h/ml)	90.31 ± 10.79	89.66 ± 16.52	87.27 ± 14.00
K_{12} (h^{-1})	6.02 ± 6.56	–	–
K_{21} (h^{-1})	4.61 ± 3.86	–	–
K_{12}/K_{21}	0.89 ± 0.76	–	–
$t_{½(d)}$ (h)	0.35 ± 0.57	–	–
V_{area} (l/kg)	0.14 ± 0.08	–	–
$V_{(d(ss))}$ (l/kg)	0.21 ± 0.05	–	–
K_a (h^{-1})	–	6.98 ± 2.71	1.28 ± 1.12*
$t_{½(a)}$ (h)	–	0.11 ± 0.04	0.80 ± 0.43*
T_{max} (h)	–	0.49 ± 0.15	1.68 ± 0.45*
C_{max} (μg/ml)	–	27.21 ± 7.67	15.57 ± 3.16*
Cl_B (l/h/kg)	0.11 ± 0.01	–	–
$t_{½}$ (h)	1.35 ± 0.25	2.10 ± 0.92	2.26 ± 0.69*†
F (%)	–	99.69 ± 18.57	96.52 ± 8.42

*Significantly different ($P < 0.05$)
†Statistically differences IV vs SC
C_1, C_2 = y-axis intercept terms; $C_{p(0)}$ = serum concentration at 0 time; λ_1 = distribution rate constant; λ_2 = elimination rate constant; $AUC_{(0-\infty)}$ = area under the serum concentration vs time curve from 0 to infinite; K_{12} = rate constant for passage from central to peripheral compartment; K_{21} = rate constant for passage from peripheral to central compartment; V_{area} = volume of distribution during pseudo-equilibrium; $V_{(d(ss))}$ = volume of distribution at steady state; K_a = absorption rate constant; $t_{½(a)}$ = absorption half-life; $t_{½(d)}$ = distribution half-life; T_{max} = time of maximum concentration; C_{max} = maximum concentration; Cl_B = body clearance; $t_{½}$ = elimination half-life; F = bioavailability

Observed intersubject variability in the distribution process is not unexpected. For most drugs, distribution is the pharmacokinetic process with the largest intersubject variability as it is related to the characteristics of the individual, such as the perfusion rate of different tissues by blood, the concentration of plasma proteins, hematocrit, body composition, tissue density and genetic variants of transporter proteins.[18]

Meropenem elimination in cats was slower than in dogs (Cl_B, 0.39 l/h/kg; $t_{½}$, 0.69 h; MRT (mean residence time), 0.88 h),[9] in ewes (Cl_B, 0.26 l/h/kg; $t_{½}$, 0.39 h; MRT, 0.73 h)[10] and in humans ($t_{½}$, 0.80–1.54 h).[3] Though mechanisms of meropenem elimination in cats have not been yet described, its clearance (0.11 ± 0.01 l/h/kg) is within the reference intervals of creatinine clearance in normal cats.[19] Interspecies differences could be due to physiological peculiarities such as the lower extracellular volume observed in cats compared with other species, which could influence the elimination half-life of drugs. Though unlikely, the administration of sedative drugs prior to antibiotic administration and blood sampling may have influenced meropenem renal excretion in cats. Furthermore, similar differences were reported for imipenem elimination between dogs and cats after IV administration, where it was faster in dogs ($t_{½}$ 0.80 ± 0.23 h)[20] than in cats ($t_{½}$ 1.17 h).[21]

Comparison of extravascular administration routes showed that when administered intramuscularly meropenem is more rapidly absorbed and eliminated. A similar situation was observed in ewes and in dogs.[9,10]

Bioavailability after IM and SC administration was similarly high for both routes (99.69% and 96.52%, respectively), without significant differences between them.

The almost complete absorption of the drug and its long permanence in plasma when administered extravascularly (especially SC) yield more desirable plasma concentration profiles than after IV administration.

Meropenem showed a low protein binding in cats, indicating that it does not impair tissue distribution. This finding is in agreement with values reported for dogs (11.87%)[9] and humans (2–8%).[3,22]

Considering that for carbapenems a T >MIC 30–40% of the dosage interval has been established as optimal for bactericidal action,[5,6] the obtained results indicate that meropenem administered at 10 mg/kg every 12 h would

be effective against bacteria with MIC values of 6 µg/ml, 7 µg/ml and 10 µg/ml for IV, IM and SC administration, respectively. Because SC administration produced the longest time above the MIC, this may be the preferred route in order to maximize the T >MIC. However, clinical studies are needed to confirm the superiority of this route of administration.

Conclusions

Based on the observed results meropenem administered to cats at a dose of 10 mg/kg q12h reaches a therapeutic target against bacteria with MIC values of 6 µg/ml, 7 µg/ml and 10 µg/ml for IV, IM and SC administration, respectively. However, clinical trials are necessary to confirm clinical efficacy of the proposed dosage regimen.

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