Serum Bactericidal Activities and Comparative Pharmacokinetics of Meropenem and Imipenem-Cilastatin

MICHAELA DREETZ,¹ JÜRIG HAMACHER,¹ JÖRG ELLER,¹ KLAUS BORNER,² PETER KOEPPE,³
TOM SCHABERG,¹ AND HARTMUT LODE^{1*}

Department for Chest and Infectious Diseases, City-Hospital Zehlendorf,¹ Institute of Clinical Chemistry and Biochemistry,² and Department of Medical Physics, Benjamin Franklin Klinikum,³ Freie Universität Berlin, Berlin, Germany

Received 12 January 1995/Returned for modification 18 June 1995/Accepted 5 October 1995

The pharmacokinetics and serum bactericidal activities (SBAs) of imipenem and meropenem were investigated in a randomized crossover study. Twelve healthy male volunteers received a constant 30-min infusion of either 1 g of imipenem plus 1 g of cilastatin or 1 g of meropenem. The concentrations of the drugs in serum and urine were determined by bioassay and high-pressure liquid chromatography. Pharmacokinetic parameters were based on an open two-compartment model and a noncompartmental technique. At the end of infusion, the mean concentrations of imipenem and meropenem measured in serum were 61.2 ± 9.8 and 51.6 ± 6.5 mg/liter, respectively; urinary recoveries were $48.6\% \pm 8.2\%$ and $60.0\% \pm 6.5\%$ of the dose in 12 h, respectively; and the areas under the concentration-time curve from time zero to infinity were 96.1 ± 14.4 and 70.5 ± 10.3 mg · h/liter, respectively ($P \leq 0.02$). Imipenem had a mean half-life of 66.7 ± 10.4 min; that of meropenem was 64.4 ± 6.9 min. The volumes of distribution at steady state of imipenem and meropenem were 15.3 ± 3.3 and 18.6 ± 3.0 liters/70 kg, respectively, and the mean renal clearances per 1.73 m^2 were 85.6 ± 17.6 and 144.6 ± 26.0 ml/min, respectively. Both antibiotics were well tolerated in this single-dose administration study. The SBAs were measured by the microdilution method of Reller and Stratton (L. B. Reller and C. W. Stratton, *J. Infect. Dis.* 136:196–204, 1977) against 40 clinically isolated strains. Mean reciprocal bactericidal titers were measured 1 and 6 h after administration. After 1 and 6 h the median SBAs for imipenem and meropenem, were 409 and 34.9 and 97.9 and 5.8, respectively, against *Staphylococcus aureus*, 19.9 and 4.4 and 19.4 and 4.8, respectively, against *Pseudomonas aeruginosa*, 34.3 and 2.2 and 232 and 15.5, respectively, against *Enterobacter cloacae*, and 13.4 and 2.25 and 90.7 and 7.9, respectively, against *Proteus mirabilis*. Both drugs had rather short biological elimination half-lives and a predominantly renal route of elimination. Both carbapenems revealed high SBAs against clinically important pathogens at 1 h; meropenem had a higher SBA against *E. cloacae* and *P. mirabilis*, and the SBA of imipenem against *S. aureus* was greater than the SBA of meropenem.

β -Lactam antibiotics are widely used for the treatment of various infectious diseases because of their potent antimicrobial activities as well as their favorable adverse effect profiles (21). Imipenem, the first clinically acceptable carbapenem, is characterized by its broad antimicrobial spectrum, including *Pseudomonas aeruginosa* (11). Its extensive renal metabolism by the dehydropeptidase-I (DHP-I) and nephrotoxic potential require a combination with cilastatin at a fixed ratio of 1:1. Meropenem is the first DHP-I-stable carbapenem (4) and is currently undergoing extensive clinical trials. The data emerging from clinical trials and in vitro studies with animals and human volunteers confirm the potential of meropenem for the treatment of a wide range of bacterial infections (7, 14, 26, 37). The chemical structures of imipenem and meropenem are shown in Fig. 1. The present study was performed to determine and compare the basic pharmacokinetic data and the serum bactericidal activities (SBAs) of these two carbapenem derivatives.

MATERIALS AND METHODS

Volunteers. A total of 12 healthy males participated in the study. All volunteers were Caucasians, and none of the volunteers had known allergies to anti-

microbial agents. Informed written consent was obtained from all volunteers. The study was approved by the local ethical committee according to German law. None of the volunteers took any other antimicrobial agent or drug during the 2 weeks preceding the study or during the study. The subjects were determined to be healthy by medical history, physical examination, and laboratory screening, all of which were conducted before the study, between days 1 and 2 of the study, and after the study. The volunteers fasted 12 h before drug administration (solid food as well as fluids), no tobacco, coffee, or tea was allowed, and they avoided all alcoholic beverages during the 24 h before antibiotic infusion. The mean age of the volunteers was 29.4 ± 6 years, the mean body weight was 80.3 ± 7.2 kg, the mean body surface area was $2.02 \pm 0.09 \text{ m}^2$, and the mean creatinine clearance was 112 ± 12.9 ml/min/ 1.73 m^2 .

Dosing. In an open randomized crossover study design, the volunteers received a single dose of 1 g of imipenem plus 1 g of cilastatin (batch CH.-B. H-A005, Zienam; MSD Sharp & Dohme GmbH, Munich, Germany) or 1 g of meropenem (batch CH.-B 59379/93; Zeneca, Plankstadt, Germany) and then the other drug regimen after a washout period of 9 weeks. For intravenous administration, both drugs were dissolved in 200 ml of 0.9% sodium chloride and were constantly infused over a 30-min period into a peripheral vein by an infusion pump (B. Braun, Melsungen, Germany). The fasting state was maintained for 2 h after drug administration.

Sampling. Samples were taken for antibiotic assays (serum for SBA, plasma for pharmacokinetics) before dosing and at 0, 15, 30, 45, 60, and 90 min and 2, 2.5, 3, 4, 5, 6, 7, and 8 h after completion of the intravenous infusion. The plasma samples obtained after imipenem-cilastatin infusion were stabilized with an equal volume of 0.5 M 2-(N-morpholine)ethansulfonic acid (pH 6.0). All samples were immediately stored on ice, centrifuged for 20 min at 4°C , shock frozen, and stored at -80°C . All volunteers started the study with empty bladders and voided to provide the last urine sample. Urine samples obtained after imipenem-cilastatin infusion were stabilized with an equal volume of 1 M morpholinepropane-sulfonic acid (MOPS; pH 6.8). The urine samples were collected at time periods of 0 to 3, 3 to 6, and 6 to 12 h after the end of infusion and were immediately shock frozen.

HPLC. Meropenem was determined by a high-pressure liquid chromatography (HPLC) method modified from the method of Nilsson-Ehle et al. (27). The

* Corresponding author. Mailing address: Department for Chest and Infectious Diseases, City-Hospital Zehlendorf/Heckeshorn, affiliat. Freie Universität Berlin, Zum Heckeshorn 33, 14109 Berlin, Germany. Phone: 0049 30 8002 2223. Fax: 0049 30 8002 2623.

FIG. 1. Chemical structures of imipenem, cilastatin, and meropenem.

analyte was separated by reversed-phase chromatography in a mobile phase consisting of 9 to 12% (vol/vol) acetonitrile and aqueous phosphate buffer (10 mmol/liter; pH 6.65). The A_{296} (plasma) or A_{310} (urine) was recorded. Peak heights were used for calculation of the concentrations, referring to external calibrators. Serum proteins were precipitated by the addition of acetonitrile that also contained hydroxyethylthiophylline as an internal standard. Acetonitrile was subsequently back-extracted with dichloromethane. Urine samples were diluted only 1:20 (vol/vol) with MOPS buffer (pH 6.5). Samples were kept at 4 to 10°C during all manipulations. The detection limit of meropenem was 0.16 mg/liter for plasma and <0.25 mg/liter for urine. The linear range was from 0.5 to 75 mg/liter for plasma and from 26 to 1,500 mg/liter for urine. The within-series precision (coefficient of variation) ranged from 2.7 to 6.4% for plasma and from 3.5 to 5.9% for urine, and the between-series precision ranged from 5.2 to 8.2% for plasma and from 2.5 to 6.7% for urine. Recoveries from plasma were 101.3 and 104.4% and 90.7 and 100.1% (urine) for meropenem and imipenem, respectively. Specificity was confirmed by complete enzymatic hydrolysis with β -lactamase type II from *Bacillus subtilis*. Comparison of the results by this method with microbiological assay results by means of mean linear regression analysis (1) yielded the following results: for plasma, y (bioassay) = $1.001 \cdot x$ (HPLC) - 0.05 mg/liter; for urine, y (bioassay) = $1.077 \cdot x$ (HPLC) - 8.2 mg/liter. The metabolite of meropenem (15) was determined in urine by ion-pair reversed-phase chromatography. The A_{210} was used for detection. The mobile phase consisted of a mixture of tetrabutylammonium phosphate solution (5 mmol/liter; pH 6.8) and acetonitrile (95/5 [vol/vol]). The method was calibrated with solutions of meropenem that were treated with β -lactamase from *B. subtilis*.

The determination of imipenem by HPLC was adopted from the method by Nilsson-Ehle et al. (27). The analyte was separated by isocratic reversed-phase chromatography in a mobile phase consisting of sodium phosphate buffer (pH 6.5) containing 3% acetonitrile. The A_{313} of the eluate was recorded. Plasma was diluted with an equal volume of morpholineethansulfonic acid buffer (pH 6.5) and was injected directly onto the column. Urine was diluted with MOPS buffer (pH 6.5) and was injected onto the column. All samples were kept in an ice bath during processing. Concentrations were calculated from peak heights by referring to external standards. The limit of detection was 0.3 mg/liter for plasma and 3.5 mg/liter for urine. The linear range was 0.5 to 10.0 mg/liter for plasma and 5 to 300 mg/liter for urine. The within-series precision (coefficient of variation) ranged from 2.2 to 3.2% for plasma and from 0.7 to 3.5% for urine. The mean recoveries from plasma were 95.0, 102.0, and 103.0% and those from urine 100.3, 101.2, and 101.3% in different control samples. Comparison of the HPLC results with the results obtained by microbiological assay by means of mean linear regression analysis (1) yielded the following results: for plasma, y (bioassay) = $0.971 \cdot x$ (HPLC) - 0.1 mg/liter; for urine, y (bioassay) = $1.045 \cdot x$ (HPLC) - 5.7 mg/liter.

For calculating the renal clearance, the value was fit to 100%.

Protein binding. The protein bindings of the two carbapenems were measured with a micropartition system (MPS-1; Amicon GmbH, Witten, Germany) by using spiked samples containing 4, 2, and 1 mg of meropenem and 2, 1, and 0.5

mg of imipenem per liter. The concentration of the free fraction in the ultrafiltration partition was determined by the agar plate diffusion technique. The centrifugation speed was $1,500 \times g$, the centrifugation time was 30 min, and the temperature was 4°C.

SBA. The SBA was detected by the microdilution method of Reller and Stratton (32). All samples were serially diluted with heat-decomplemented (56°C, 30 min) Mueller-Hinton (MH) substrate, consisting of equal parts of pooled human serum and MH bouillon, from 1:2 to 1:512 and were incubated for 18 h at 37°C with a final inoculum size of 5×10^5 organisms per ml. The inhibiting titer in serum was the highest dilution that showed no visible turbidity. A 1- μ l sample from each well showing no visible growth was subcultured onto MH agar, and the plate was incubated for 12 h at 37°C. The dilution that killed >99.9% of the initial inoculum was the SBA. In the present study, the following freshly isolated pathogens were tested against sera from all volunteers 1 h after the end of infusion (peak) and 6 h after the end of infusion: methicillin-susceptible *Staphylococcus aureus* (10 strains), *Pseudomonas aeruginosa* (10 strains), *Enterobacter cloacae* (10 strains), and *Proteus mirabilis* (10 strains).

Pharmacokinetic analysis. Pharmacokinetic parameters were calculated (i) by noncompartmental analysis and (ii) on the basis of an open two-compartment model (13, 33). (i) The area under the data (AUD) was calculated noncompartmentally by the log trapezoidal rule, corrected for body weight and reference dose. (ii) We corrected the calculated pharmacokinetic constants for infusion time as described by Loo and Riegelman (25) by using the open two-compartment model: drugs were administered into and eliminated from a central compartment only. However, reversible drug distribution from the central space occurs simultaneously into one peripheral space (25).

An iterative relative least-squares method was used to fit constants to the experimental data for the serum concentration-time curve (22–24). Serum drug concentrations were normalized for a body weight of 70 kg before determination of the pharmacokinetic parameters. The area under the curve (AUC) was calculated by using the compartmental model (AUC from time zero to infinity [$AUC_{0-\infty}$]) and the half-lives ($t_{1/2s}$) in the distribution and elimination phases. The volume of distribution at steady state (V_{ss} ; in liters per 70 kilograms [V_{ss} as a percentage of body weight]) was detected by noncompartmental analysis. The alternative for biological $t_{1/2s}$, the mean residence time (MRT), was determined by using both pharmacokinetic models (8, 20). The renal clearance was total clearance $\times$ percent recovery in urine/100.

Statistical analysis. Wilcoxon's test (signed-rank test for paired samples, two tailed) was used for statistical comparison. A P value of ≤ 0.05 was considered significant.

RESULTS

Tolerance. No abnormal physical or laboratory findings were observed. All adverse effects were mild in severity. One volunteer suffered from vertigo for about 4 min after the infusion of imipenem, but could continue participating thereafter. Two volunteers complained of moderate headaches. This was probably due to abstinence from coffee, tea, and tobacco products.

Single-dose kinetics. The drug concentrations and the pharmacokinetic results in Table 1 are given on the basis of the data from HPLC. Comparison of the results obtained by HPLC and bioassay methods showed an excellent correlation between the concentrations of meropenem and imipenem in plasma as well as in urine for imipenem (Table 1). The concentration of meropenem in urine detected by the HPLC method was slightly less than the concentration detected by the bioassay (Fig. 2). One metabolite of meropenem was found by HPLC. It was not microbiologically active, which explains the difference in the concentrations found by the two assays. Imipenem metabolites were not assayed. Predose samples of blood and urine showed no detectable activity.

A dose of 1 g of meropenem resulted in a mean peak concentration in serum of 51.6 ± 6.5 mg/liter, and a dose of 1 g of imipenem plus 1 g of cilastatin resulted in a peak concentration in serum of 61.2 ± 9.8 mg/liter after the 30-min infusion, with decreases, respectively, to 15.0 ± 2.23 and 21.0 ± 3.99 mg/liter after 1 h, 0.42 ± 0.16 and 0.82 ± 0.35 mg/liter after 6 h, and 0.15 ± 0.12 and 0.24 ± 0.12 mg/liter after 8 h (Fig. 3).

The pharmacokinetics of both drugs could be described by an open two-compartment model with a rather short $t_{1/2}$ ($t_{1/2}$ of imipenem, 66.7 ± 10.4 min; $t_{1/2}$ of meropenem, 64.4 ± 6.9 min). The mean $AUC_{0-\infty}$ of imipenem was 96.1 ± 14.4 mg $\cdot$ h/liter, and that of meropenem was 70.5 ± 10.3 mg $\cdot$ h/liter.

FIG. 2. Cumulative renal elimination of imipenem, meropenem, and the metabolite of meropenem.

These results are in close agreement with the AUD from time zero to infinity ($AUD_{0-\infty}$). The mean V_{ss} of imipenem was 15.5 ± 3.3 liters/70 kg ($23.6\% \pm 3.1\%$ of body weight), and that of meropenem was 18.6 ± 3.0 liters/70 kg ($26.6\% \pm 4.0\%$ of body weight). The MRTs of imipenem and meropenem were 85.8 ± 13.0 and 76.1 ± 7.9 min, respectively. The total body clearance (CL) of imipenem was 175.2 ± 23.1 ml/min/1.73 m², and that of meropenem was 240.1 ± 29.9 ml/min/1.73 m². More than two-thirds of the doses of both drugs were eliminated within 3 h (imipenem, $38.8\% \pm 12.6\%$; meropenem, $51.9\% \pm 9.0\%$). At 12 h after the end of infusion, the mean urinary recovery of imipenem was $48.5\% \pm 8.2\%$ of the administered dose, and that of meropenem was $60\% \pm 6.5\%$. The mean protein binding of imipenem was 8.7%, and that of meropenem was 8.0%.

SBA. At the beginning of the study we investigated the MICs and MBCs for the four different bacterial strains used for SBA determinations (Table 2). We found the mean MIC and the mean MBC of imipenem-cilastatin to be 0.003 to 0.063 and 0.003 to 0.063 mg/liter, respectively, for *S. aureus*, 0.5 to 8 and 0.5 to 16 mg/liter, respectively, for *P. aeruginosa*, 0.063 to 1 and 0.125 to 2 mg/liter, respectively, for *E. cloacae*, and 2.0 to 4.0 and 2.0 to 8.0 mg/liter, respectively, for *P. mirabilis*. The mean MIC and the mean MBC of meropenem were 0.125 to 0.25 and

FIG. 3. Mean $\pm$ standard deviation concentrations of imipenem and meropenem in plasma determined by HPLC. The drugs were given at a dose of 1,000 mg over 30 min as an intravenous infusion. —, imipenem regression; - - -, meropenem regression; ●, mean $\pm$ standard deviation imipenem concentration; □, mean $\pm$ standard deviation meropenem concentration.

TABLE 1. Pharmacokinetic parameters of imipenem-cilastatin and meropenem^a

Drug	$AUC_{0-\infty}$ (mg · h/liter)	$AUD_{0-\infty}$ (mg · h/liter)	Concn at time zero (mg/liter)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	MRT (min) ^b	V_{ss} (liters/70 kg) ^b	V_{ss} (%) of body weight ^b	V_{area} (liters/70 kg)	V_{area} (%) (liters/100 kg)	CL (ml/min/ 1.73 m ²) ^b	CL _R (ml/min/ 1.73 m ²) ^b	CL _{NR} (ml/ min/1.73 m ²) ^b	% Urinary recovery ^b	% Total urinary recovery	% Protein binding
Imipenem-cilastatin	96.1 ± 14.4	95.0 ± 14.3	61.2 ± 9.8	15.7 ± 4.7	66.7 ± 10.4	85.8 ± 13.0	15.3 ± 3.3	21.8 ± 4.7	17.2 ± 3.8	24.6 ± 5.4	175 ± 23.0	85.6 ± 17.6	90.6 ± 18.6	46.2 ± 11.0	48.6 ± 8.2	8.7
Meropenem	70.5 ± 10.3^c	69.2 ± 10.2^c	51.6 ± 6.5	17.0 ± 4.4	64.4 ± 6.5	76.1 ± 7.9	18.6 ± 3.0^c	26.6 ± 4.3^c	22.7 ± 3.4	32.4 ± 4.8	240 ± 30	144.3 ± 26.0	95.8 ± 18.4	58.7 ± 7.4^c	60.0 ± 6.5^c	8.0

^a The pharmacokinetic parameters were determined by HPLC following the administration of 1-g intravenous doses to 12 healthy male volunteers. Values are means $\pm$ standard deviations. $t_{1/2\alpha}$ and $t_{1/2\beta}$ half-lives in the distribution and elimination phases, respectively; V_{area} volume of distribution calculated from terminal elimination rate; CL, CL_R, and CL_{NR} total, renal, and nonrenal clearance, respectively; the other abbreviations are defined in the text.

^b Results were analyzed noncompartmentally.

^c $P \leq 0.05$.

TABLE 2. SBAs of imipenem and meropenem against four organisms

Drug	SBA (mean reciprocal titers)							
	<i>S. aureus</i> (n = 10)		<i>E. cloacae</i> (n = 10)		<i>P. mirabilis</i> (n = 10)		<i>P. aeruginosa</i> (n = 10)	
	1 h	6 h	1 h	6 h	1 h	6 h	1 h	6 h
Imipenem	409	35	34	2.2	13	2.25	20	4.4
Meropenem	98	5.8	232	15	91	7.9	19	4.8

0.125 to 0.5 mg/liter, respectively, for *S. aureus*, 0.063 to 2.0 and 0.125 to 4, respectively, for *P. aeruginosa*, 0.003 to 0.016 and 0.16 to 0.31 mg/liter, respectively, for *E. cloacae*, and 0.125 to 0.5 and 0.25 to 0.5 mg/liter, respectively, for *P. mirabilis*.

At 1 h after the end of infusion, the SBAs of imipenem and meropenem resulted in high mean reciprocal titers. Imipenem showed an increased mean peak titer against *S. aureus* of 409, while meropenem showed a titer four times less than that of imipenem (97.9). Both antibiotics had mean titers of 19.9 (imipenem) and 19.4 (meropenem) against *P. aeruginosa*. Meropenem offered an increased mean peak titer of 232 against *E. cloacae* and 90.7 against *P. mirabilis*, while imipenem had lower titers of 34.3 against *E. cloacae* and 13.4 against *P. mirabilis*. At 6 h after the end of infusion, imipenem-cilastatin revealed low reciprocal SBA titers against *P. aeruginosa* (4.4), *E. cloacae* (2.2) and *P. mirabilis* (2.5), whereas it was still effective against *S. aureus*, with a titer of 34.9. Low respective SBA titers of meropenem were determined against *P. aeruginosa* (4.8) and *S. aureus* (5.8) at 6 h after the end of infusion. The sera from volunteers treated with meropenem showed reduced mean titers against *P. mirabilis* (7.9) and *E. cloacae* (15.5).

DISCUSSION

Tolerance. Both drugs were well tolerated, although one volunteer suffered from a short period of vertigo and two others suffered from headaches; however, the headaches could not directly be attributed to the infusion of the drugs. The most common known side effects of imipenem-cilastatin are rashes, nausea, and vomiting (5, 9). The incidence of vomiting and nausea appears to be related to rapid infusion (6). Meropenem can be given by intravenous infusion or bolus injection without any associated nausea or vomiting in most patients (41). However, no nausea or vomiting was seen in the present study after the infusion of either drug.

Pharmacokinetics. The pharmacokinetic results for imipenem-cilastatin were comparable to earlier published data except for a lower level of renal elimination (3, 27). The pharmacokinetic results for meropenem were very similar to those reported by Bax et al. (2).

Nilsson-Ehle et al. (27) compared the two carbapenem derivatives, and their results revealed significant differences only in the volumes of distribution, whereas our study found significant ($P \leq 0.05$) differences in the AUCs, AUDs, V_{ss} s, CLs, and urinary recoveries of meropenem and imipenem. Approximately 70% of the administered dose was detected unchanged in the urine by other investigators (2, 27, 41). Our results revealed a total urine recovery of $48.6\% \pm 8.2\%$ for imipenem and $60\% \pm 6.5\%$ for meropenem. The difference in urine sampling times may explain the lower rate of urinary recovery. While Bax et al. (2) and Nilsson-Ehle et al. (27) collected urine hourly, in the study of Wise et al. (41) as well as in the present study, urine was collected at greater intervals and, conse-

quently, remained for a longer period of time in the bladder at higher temperatures. Wise et al. (41) also recorded a lower total urinary recovery than those records in the two studies mentioned above (2, 27). Imipenem and meropenem had comparable mean concentrations at the end of infusion, similar elimination $t_{1/2}$ s, and comparable MRTs. The protein binding data for imipenem and meropenem are in agreement with reports by other authors. Results for imipenem range from <10 to 20% (6). Serum protein binding studies of meropenem by ultrafiltration and microbiological assay or radioassay showed levels of binding of 12.9 and 2%, respectively (43).

SBA. The SBA test has been used for many years to monitor antibiotic therapy, but many technical variables influence the measurement of SBA, and even in patients drug levels fluctuate (29, 42). However, a serum bactericidal titer of $\geq 1:8$ is suggested to be associated with a significantly better therapeutic outcome in febrile cancer patients (19), and in patients with granulocytopenia, a titer of $\geq 1:16$ seems to be necessary for the treatment of gram-negative bacillary bacteremia (31, 32, 36). In the present study the SBA test took into account the ability of healthy volunteers to distribute, eliminate, and metabolize the antibiotic as well as influence the bacterial growth by additional serum activity.

In vitro studies carried out in 41 European countries (10) showed results in favor of meropenem over imipenem-cilastatin against members of the family *Enterobacteriaceae*, *Haemophilus influenza*, *P. aeruginosa*, and other species including *Pseudomonas cepacia*. Our study showed reciprocal titers of meropenem more than sixfold higher than those of imipenem against *E. cloacae* and *P. mirabilis*. Because of the rather short elimination $t_{1/2}$ s of the tested antimicrobial agents, all serum bactericidal titers were considerably reduced by 6 h after the end of infusion. At 6 h after the infusion of meropenem, titers against *E. cloacae* and *P. mirabilis* were 1:15.5 and 1:7.9, respectively, whereas titers after the infusion of imipenem were 1:2.2 and 1:2.5, respectively. Results for *P. aeruginosa* revealed titers of 1:19.9 after 1 h and 1:4.4 after 6 h for imipenem and titers of 1:19.4 after 1 h and 1:4.8 after 6 h for meropenem. The results of in vitro studies indicate that meropenem has two- to fourfold greater activity than imipenem against *P. aeruginosa* (12, 38). The serum bactericidal titers of imipenem-cilastatin were more than fourfold more effective than those of meropenem against *S. aureus*. At 6 h after the end of infusion we observed titers against *S. aureus* of 1:34.9 for imipenem-cilastatin and 1:5.8 for meropenem. Kayser et al. (18) reported that imipenem-cilastatin and meropenem have comparable in vitro activities against *S. aureus*. In general, SBA titer results reflected the different activities of the two carbapenem derivatives against *E. cloacae* and *S. aureus*. Clinical data indicate that meropenem is as effective as imipenem-cilastatin in the treatment of community-acquired respiratory tract infections, hospital-acquired lower respiratory tract infections, intra-abdominal infections, and skin and skin structure infections (16, 17, 28, 34, 35, 39, 40).

Conclusion. The present study demonstrated that the new carbapenem derivative meropenem has pharmacokinetic characteristics nearly identical to those of imipenem-cilastatin. However imipenem-cilastatin had a greater AUC than meropenem, depending on lower renal and total clearances.

The SBAs of the drugs against 40 clinical strains indicated that meropenem has somewhat greater activity against *E. cloacae* and *P. mirabilis*, while imipenem-cilastatin has better activity against *S. aureus*.

ACKNOWLEDGMENTS

We gratefully acknowledge the technical assistance of Ellen Borner, Margot Rau, and Jessica Vöckler.

This work was supported by Zeneca GmbH, Plankstadt, Germany.

REFERENCES

- Averdunk, R., and K. Borner. 1970. Korrelation der Thromboplastinzeiten bei Dicumarol-behandelten Patienten unter Verwendung verschiedener Thrombokinase-Präparate. *Z. Klin. Chem. Klin. Biochem. Dis.* **10**:85–88.
- Bax, R. P., W. Bastain, A. Featherstone, D. M. Wilkinson, M. Hutchinson, and S. J. Haworth. 1989. The pharmacokinetics of meropenem in volunteers. *J. Antimicrob. Chemother.* **24**(Suppl. A):311–320.
- Buckley, M. M., R. Brogden, L. Barradell, and K. Goa. 1992. Imipenem/cilastatin: a reappraisal of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* **44**:408–444.
- Burman, L. A., I. Nilsson-Ehle, M. Hutchinson, M. Haworth, S. J. Haworth, and S. R. Norrby. 1991. Pharmacokinetics of meropenem and its metabolite ICI 213,689 in healthy subjects with known renal metabolism of imipenem. *J. Antimicrob. Chemother.* **27**:219–224.
- Calandra, G. B., F. M. Ricci, C. Wang, and K. R. Brown. 1988. The efficacy results and safety profile of imipenem/cilastatin from clinical research trials. *J. Clin. Pharmacol.* **28**:120–127.
- Clisshold, S. P., P. A. Tood, and D. M. Campoli-Richards. 1987. Imipenem/cilastatin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* **33**:183–241.
- Davy, P., A. Davies, D. Livermore, D. Speller, and P. J. Daly. 1989. Meropenem (SM7338)—a new carbapenem. *Antimicrob. Chemother.* **24**(Suppl. A):1–320.
- Dettili, L. 1977. Elimination kinetics and dosage adjustment of drugs in patients with kidney disease. *Prog. Pharmacol.* **17**:90–96.
- Duque, A., J. Altamiras, C. Garcia-Cases, and P. Vidal. 1991. Vertigo caused by intravenous imipenem/cilastatin. *DICP Ann. Pharmacother.* **25**:1009.
- Edwards, J. R., and P. J. Turner. 1992. Antibacterial activity of meropenem against 22,000 isolates tested in 41 European studies, abstr. 331, p. 250. *In Abstracts of the 8th Mediterranean Congress on Chemotherapy. Mediterranean Society of Chemotherapy, Zagreb.*
- Fukuhara, H., N. Kusano, H. Nakamura, H. Kaneshima, Y. Irabu, K. Shimozaki, K. Kitukawa, Y. Shigeno, A. Saito, T. Kakazu, et al. 1991. Clinical evaluation of imipenem/cilastatin sodium in internal medicine. *Jpn. J. Antibiot.* **44**:877–885.
- Garcia-Rodriguez, J. A., J. E. Garcia-Sanchez, J. L. Munoz-Bellido, E. Garcia-Sanchez, and M. I. Garcia-Garcia. 1991. In-vitro activity of meropenem, a new carbapenem, against imipenem-resistant *Pseudomonas aeruginosa* and *Xanthomonas maltophilia*. *J. Chemother.* **3**:143–146.
- Greenblatt, D. S., and J. Koch-Weser. 1975. Clinical pharmacokinetics. *N. Engl. J. Med.* **193**:702–705, 964–970.
- Harabe, A., Y. Kawai, K. Kanazawa, M. Otsuki, and T. Nishino. 1992. In vitro and in vivo antibacterial activities of meropenem, a new carbapenem antibiotic. *Drugs Exp. Clin. Res.* **18**:37–46.
- Harrison, M. P., S. J. Haworth, S. R. Moss, D. M. Wilkinson, and A. Featherstone. 1993. The disposition and metabolic fate of ¹⁴C-meropenem in man. *Xenobiotica* **11**:1311–1323.
- Huizinga, W. K. J., L. W. Baker, B. Warren, J. Chipponi, P. Valeur, J. Hoogkamp-Korstanje, and S. Karren. 1993. Antibiotic monotherapy with meropenem in the surgical management of intra-abdominal infections, abstr. 536, p. 217. *In Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.*
- Kanellakopoulou, K., H. Giamarellou, P. Papdorthomakos, H. Tsiplas, J. Chloroyiannis, R. Theakou, and P. Sfikakis. 1993. Meropenem versus imipenem/cilastatin in the treatment of intraabdominal infections requiring surgery. *Eur. J. Clin. Microbiol. Infect. Dis.* **12**:449–453.
- Kayser, F. H., G. Morenzoni, A. Strassle, and K. Hadorn. 1988. Activity of meropenem against gram-positive bacteria. *J. Antimicrob. Chemother.* **24**(Suppl. A):101–112.
- Klastersky, J., D. Didier, G. Swing, and D. Werts. 1974. Antibacterial activity in serum and urine as a therapeutic guide in bacterial infections. *J. Infect. Dis.* **129**:187–193.
- Klotz, U. 1984. *Klinische Pharmakokinetik*, 2nd ed. G. Fischer, Stuttgart, Germany.
- Knothe, H. 1991. Antibiotic usage for initial empirical treatment of infections in hospitalized patients in West Germany. *Infection* **19**:127–130.
- Koepe, P., and C. Hamann. 1978. Zwei Methoden zur Parameterschätzung nicht linearer Regressionsfunktionen bei fehlerhaften Messdaten. *EDV Med. Biol.* **9**:112–117.
- Koepe, P., and C. Hamann. 1980. A program for nonlinear regression analysis to be used on desk-top computer. *Comput. Prog. Biomed.* **12**:121–128.
- Koepe, P., and D. Hoeffler. 1972. Die Verwendung eines Digitalrechners zur Entwicklung von Dosierungsempfehlungen für die Antibiotikatherapie. *Arzneim.-Forsch.* **21**:311–319.
- Loo, J. C. K., and S. Riegelman. 1970. Assessment of pharmacokinetic constants from postinfusion blood curves obtained after i.v. infusion. *J. Pharm. Sci.* **59**:53–57.
- Murray, P. R., and A. C. Niles. 1990. In vitro activity of meropenem (SM-7338), imipenem, and five other antibiotics against anaerobic clinical isolates. *Diagn. Microbiol. Infect. Dis.* **13**:57–61.
- Nilsson-Ehle, I., M. Hutchinson, S. J. Haworth, and S. R. Norrby. 1991. Pharmacokinetics of meropenem compared to imipenem/cilastatin in young, healthy males. *Eur. J. Clin. Microbiol. Infect. Dis.* **10**:85–88.
- Nord, C. E. 1993. Meropenem versus imipenem/cilastatin for treatment of intraabdominal infections, abstr. 641, p. 236. *In Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.*
- Pien, F. D., and K. L. Vosti. 1974. Variation in performance of the serum bactericidal test. *Antimicrob. Agents Chemother.* **6**:330–333.
- Reeves, D. S., and M. J. Bywater. 1976. Assay of antimicrobial agents, p. 21–78. *In J. de Louvois (ed.), Selected topics in clinical bacteriology. Balliere Tindall, London.*
- Reller, L. B. 1986. The serum bactericidal test. *Rev. Infect. Dis.* **8**:803–808.
- Reller, L. B., and C. W. Stratton. 1977. Serum dilution test for bactericidal activity. II Standardization and correlation with antimicrobial assays and susceptibility tests. *J. Infect. Dis.* **136**:196–204.
- Ritschel, W. A., and T. W. Robinson. 1980. *Handbook of basic pharmacokinetics*, 2nd ed. Drug Intelligence Publications, Inc., Washington, D.C.
- Sartoretti, C. H. R., B. Attinger, J. Schilling, F. Largaider, and S. Geroulanos. 1992. Meropenem versus imipenem/cilastatin in the treatment of abdominal infections, abstr. 1583, p. 374. *In Program and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.*
- Smith, J., A. Muzik, A. Motamedi, J. Lami, J. Hopkins, and S. Wilson. 1991. Randomized comparative study of meropenem versus imipenem/cilastatin in the treatment of skin and skin structure infections, abstr. 612, p. 201. *In Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.*
- Stratton, C. W., P. W. Weinstein, and L. B. Reller. 1982. Correlation of serum bactericidal activity with antimicrobial agent level and minimal bactericidal concentration. *J. Infect. Dis.* **145**:160–168.
- Turner, P. J., and J. R. Edwards. 1993. European multicentre comparison of in vitro activity of meropenem (MEM), imipenem (IPM), and cephalosporins, gentamicin, metronidazole and clindamycin, abstr. 720, p. 190. *In Program and abstracts of the 6th European Congress of Clinical Microbiology and Infectious Disease. European Society of Clinical Microbiology and Infectious Diseases, Munich.*
- Turner, P. J., and J. R. Edwards. 1993. The activity of meropenem and comparators against *Pseudomonas aeruginosa* strains isolated throughout Europe. *In Abstracts of the 18th International Congress on Chemotherapy, Stockholm. International Society of Chemotherapy, Oslo.*
- Vetter, N. 1992. Efficacy of meropenem in the treatment of respiratory tract infection: a comparative evaluation, abstr. 232, p. 175. *In Abstracts of the 8th Mediterranean Congress on Chemotherapy. Mediterranean Society of Chemotherapy, Zagreb.*
- Vetter, N. 1993. Meropenem as empiric monotherapy for the treatment of hospital acquired lower respiratory tract infection, abstr. 70, p. 134. *In Program and abstracts of the 18th International Congress on Chemotherapy, Stockholm. International Society of Chemotherapy, Oslo.*
- Wise, R., M. Logan, M. Cooper, J. P. Ashby, and J. M. Andrews. 1990. Meropenem pharmacokinetics and penetration into inflammatory exudate. *Antimicrob. Agents Chemother.* **34**:1515–1517.
- Wolfson, J. S., and M. N. Swartz. 1985. Serum bactericidal activity as a monitor of antibiotic therapy. *N. Engl. J. Med.* **312**:968.
- Zeneca GmbH. 1993. *Laboratory manual: meropenem*. Zeneca GmbH, Plankstadt, Germany.