An Open, Randomized, Single-Center, Crossover Pharmacokinetic Study of Meropenem after Intraperitoneal and Intravenous Administration in Patients Receiving Automated Peritoneal Dialysis

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The objective of this study was to determine the pharmacokinetic profile of meropenem in automated peritoneal dialysis (APD) patients. In 6 patients without peritonitis, a single dose of 0.5 g of meropenem was applied intraperitoneally (i.p.) or intravenously (i.v.) and concentrations in serum and dialysate were measured at specified intervals over 24 h with high-performance liquid chromatography-mass spectrometry. The mean maximum concentrations of meropenem in serum (Cmax) were 27.2 mg/liter (standard deviation [SD], ±6.9) and 10.1 mg/liter (SD, ±2.5) and in dialysate were 3.6 mg/liter (SD, ±2.3) and 185.8 mg/liter (SD, ±18.7) after i.v. and i.p. administrations, respectively. The mean areas under the curve from 0 to 24 (AUC0–24) of meropenem in serum were 173.5 mg · h/liter (SD, ±29.7) and 141.4 mg · h/liter (SD, ±37.5) (P = 0.046) and in dialysate were 42.6 mg · h/liter (SD, ±20.0) and 623.4 mg · h/liter (SD, ±84.1) (P = 0.028) after i.v. and i.p. administrations, respectively. The ratios for dialysate exposure over plasma exposure after i.v. and i.p. treatments were 0.2 (SD, ±0.1) and 4.6 (SD, ±0.9), respectively (P = 0.031). A mean target value of 40% T>MIC (time for which the free meropenem concentration exceeds the MIC) for clinically relevant pathogens with EUCAST susceptibility breakpoints of 2 mg/liter was reached in serum after i.p. and i.v. administrations and in dialysate after i.p. but not after i.v. administration. The present data indicate that low i.p. exposure limits the i.v. use of meropenem for PD-associated peritonitis. In contrast, i.p. administration not only results in superior concentrations in dialysate but also might be used to treat systemic infections.

Peritonitis is still the most important complication in patients on peritoneal dialysis (PD) and is a significant cause of hospitalization, treatment failure, and even mortality (1). In cases of PD-related peritonitis, intraperitoneal (i.p.) application of antibiotics is recommended due to higher concentrations at the site of infection than with intravenous (i.v.) application (2). Moreover, i.p. application of antimicrobial agents is a feasible form of antimicrobial treatment in PD patients with systemic bacterial infection.

In general, there exist two main modalities of performing PD. In continuous ambulant peritoneal dialysis (CAPD) patients, 4 to 6 manual exchanges of the intra-abdominal dialysate fluid are performed, with a dwell time of 4 to 8 h. In automated PD (APD) patients, dialysate exchanges are performed automatically by a cycler device, usually done at home during the night with various numbers of fluid changes and dialysate volumes. During the day, the abdominal cavity is filled with dialysate fluid for a long dwell.

Regarding i.p. dosing recommendations for antimicrobial therapy in PD patients, most of the available pharmacokinetic (PK) data derive from studies performed with patients on CAPD, whereas pharmacokinetic data from patients on APD treatment are rare (3–6). The drug dosing regimen established for CAPD, however, may not be applicable to APD patients, since there are substantial differences in the dialysate volumes and dwell times between the two treatment modalities. Increased peritoneal clearance of antibiotics and insufficient intraperitoneal drug concentration during rapid cycling periods of the dialysate fluid are possible reasons for treatment failure of peritonitis in APD patients (6).

For empirical treatment of PD-associated peritonitis, current guidelines advocate the i.p. use of cephalosporins, such as cefepime or a combination of cefazolin and ceftazidime (2). An increasing number of multidrug-resistant bacteria, however, has directed the interest to antimicrobial agents with broader activity. Therefore, carbapenems, in particular meropenem, have been increasingly used for initial empirical therapy of PD-associated peritonitis. It was shown that i.p. application of meropenem is feasible to treat peritonitis in PD patients (7, 8). However, dosing recommendations for intraperitoneal meropenem are based on two single case reports of patients on CAPD (7, 8), and no pharmacokinetic data for patients on APD are available.

Therefore, the present study set out to investigate if intermittent i.p. application of meropenem is appropriate for the treatment of peritonitis and achieves adequate blood levels for effective...
systemic antimicrobial therapy compared to i.v. administration in patients with APD.

MATERIALS AND METHODS

An open, randomized, single-center crossover descriptive PK study with 1 group (EDURACT no. 2013-004985-32) with six patients on APD without peritonitis was performed. The clinical study was conducted at the 1st Medical Department of the University Hospital St. Poelten, the samples were analyzed at the Department of Pharmacognosy, University of Vienna. Meropenem was administered for study purpose only and not for infection. The study was done in accordance with the actual International Conference on Harmonization good clinical practice (ICH-GCP) guidelines and the Declaration of Helsinki and was authorized by the Austrian Agency for Health and Food Safety (AGES). The study protocol was approved by the Ethical Board of Lower Austria. Written informed consent was obtained from each patient enrolled.

The inclusion criteria for study enrollment were an age between 18 and 85 years and stability on APD for at least 3 months prior to the start of the study. Exclusion criteria were any systemic infection, peritonitis, or catheter-related infection which required antibiotic treatment within 2 months prior to the start of the study, severe hepatic impairment (Child-Pugh class C), and allergy or hypersensitivity to the study drug.

Patients were randomized for either i.v. or i.p. application of a single dose of 0.5 g of meropenem (Hospira, Munich, Germany) for the first period and the alternative application scheme for the second period, with a washout time of at least 7 days between the two periods. At the beginning of each study day, complete drainage of the abdominal fluid of each patient was performed. Afterwards, patients received 0.5 g of meropenem either intraperitoneally via 1.5 liters of the icodextrin-containing dialysate solution Extraneal (7.5% icodextrin; Baxter Healthcare Corp., Deerfield, IL), which was instilled into the peritoneal cavity over a 10-min period or intravenously over a 30-min period. After a long dwell of the dialysate solution (15 h), patients underwent an APD treatment for 9 h consisting of 6 cycles (Fig. 1). The cycle volume was 2,000 ml (Home Choice Pro Cycler), using Physioneal 40, 2.5- and 5-liter bags (1.36% to 3.86% glucose; Baxter Healthcare Corp.). The average glucose concentrations used during APD treatment ranged from 1.36% to 2.72% depending on the peritoneal ultrafiltration rate and residual urine output of the individual patient in order to keep the fluid balance.

Further data collected included date of birth, age, sex, height, weight, body mass index (BMI), and the date peritoneal dialysis was initiated, as well as comedication and medical history.

Blood samples and dialysate fluid samples were obtained at baseline (directly before application of meropenem), at the end of the i.v. infusion or i.p. administration, and at 1, 2, 3, 4, 6, 9, 12, and 15 h after the start of application. Afterwards, sampling of dialysate fluid and venous blood was performed at the end of each short cycle of dialysis, i.e., approximately every 1.5 h after start of cycler treatment up to 24 h after drug application. Approximately 5 ml of venous blood for the measurement of plasma drug levels was drawn at each time point. Blood was collected into lithium-heparin tubes (Vacuette lithium-heparin). Further, for patients with residual renal function, 5 ml of urine was drawn from a 24-h urine sample. Blood samples, urine samples, and dialysate samples were kept on ice for a maximum of 10 min. Blood samples were centrifuged at 4°C and 3,500 rpm for 10 min, cells were discharged, and plasma samples were obtained. Plasma and dialysate samples were divided into two aliquots of approximately 1 ml and were snap-frozen at −20°C. Thereafter, samples were stored at −80°C until analysis.

Residual glomerular filtration rate (GFR) values were calculated according to the formula in the Dialysis Outcomes Quality Initiative (DOQI) guidelines, using PD Adequacy 2.0 for Windows software (Baxter Healthcare Corp., Deerfield, IL). GFR = (residual urea clearance + residual creatinine clearance)/2. Residual urea clearance = (urine concentration/serum blood urea nitrogen\[BUN\] concentration) × urine volume (in milliliters)/1,440. Residual creatinine clearance = (urine concentration/serum creatinine concentration) × urine volume (in milliliters)/1,440. Urine volume and urine concentration were measured in 24-h urine samples (9).

Study drug concentrations in plasma, dialysate, and urine samples were analyzed using an established high-performance liquid chromatography (HPLC)-mass spectrometry (MS) method. To 100-μl plasma or urine samples 300 μl of methanol was added and mixed, and the samples were centrifuged at 15,000 rpm. One hundred microliters of the supernatant was diluted with 400 μl of water and analyzed (5 μl). Dialysate fluid samples were analyzed directly (5 μl). Meropenem was quantified using HPLC-tandem MS (MS/MS) on an Ultimate 3000 RSLC-series system (Dionex, Germering, Germany) coupled to a triple quadrupole mass spectrometer (AB Sciex Instruments API 4000) equipped with an orthogonal electrospray ionization (ESI) source operated in positive mode.

Liquid chromatography (LC) separation was performed on an Acclaim RSLC 120 C18 column (3 μm; 150- by 2.1-mm inside diameter [i.d.]; Thermo Fisher Scientific), preceded by an Acclaim 120 C18 guard cartridge (5 μm; 10- by 2-mm i.d.; Thermo Fisher Scientific), at a flow rate of 0.5 ml/min and a column temperature of 25°C. The mobile phase consisted of a linear gradient mixed from 0.1% aqueous formic acid (mobile phase A) and acetonitrile (mobile phase B). The gradient ranged from 5% mobile phase B at 0 min to 25% mobile phase B in 7.5 min, purging with 95% mobile phase B for 2 min and then again with 5% mobile phase

FIG 1 Schematic presentation of the sampling schedule.
B to equilibrate the column for 4 min before application of the next sample (total analysis time, 13.5 min), meropenem eluted at 4.74 min. Selective and sensitive detection and quantification were carried out using MS/MS fragmentation of meropenem, giving a quasimolecular ion at m/z 384 [M+H]+. Multiple reaction monitoring m/z 384/141 was used for calibration curves with external standard meropenem (injection volume, 5 μL) to give a linear concentration range from 0.1 ng/ml to 10,000 ng/ml (correlation coefficient, 0.99).

The triple quadruple mass spectrometer operated with the following parameters: ESI positive, IS 5500, EP 10, CUR 5, GS1 40, GS2 40, TEM 500°C, CAD 4, CEM 2100, DF –25, DP 56, CE 25, CXP 12, dwell 300 ms.

Pharmacokinetic parameters were calculated using a commercially available computer program (Kinetika 3.0; Innaphase). Maximum concentration (C_max) in plasma, time to maximum plasma concentration (t_max), terminal elimination half-life (1/2t), and area under the concentration-time curve from 0 to 24 h (AUC_0–24) were calculated from non-fitted data by employing the trapezoidal rule for all compartments. Additionally, the apparent total body clearance (CL) was calculated by dividing the dose of meropenem by AUC_∞–τ and the apparent meropenem volume of distribution (V) during the beta-phase was determined. V and CL are only given for serum after i.v. application and for peritoneal fluid after i.p. administration.

The ratios for dialysate exposure and plasma exposure after i.v. and i.p. treatment, respectively, were calculated using area under the concentration-time curves from 0 to 24 h of respective compartments.

For meropenem, the time for which the free meropenem concentration exceeds the MICs for relevant pathogens (T>MIC) can be used to predict antimicrobial action, which means that optimal bacterial killing is observed when the free concentration is moderately higher than the MIC for the pathogen for a period of 40% of the dosing interval. For meropenem, the protein binding, however, is only 2% and was therefore neglected in the present study.

T>MIC was determined for individual patients for MICs of 2 mg/liter, 4 mg/liter, and 8 mg/liter and are expressed as percentages of a dosing interval of 24 h (9). Therefore, percent (T>MIC) was calculated according to the equation ln[dose/(V × MIC)] × [t1/2(ln(2))/ (100/DI)] as proposed by Turnidge (10), where DI is dosing interval.

The Wilcoxon matched-pairs test was used to compare the ratios for dialysate exposure over plasma exposure and the AUC values between study periods (i.e., i.v. and i.p. applications) for serum and dialysate, respectively. Statistical analysis was performed by means of a commercially available statistical program (IBM SPSS Statistics 20; IBM, Armonk, NY).

RESULTS

The demographic data for the six patients enrolled are shown in Table 1. The mean age was 58.5 years (standard deviation [SD], ±11.3) years. Patients were on PD for 42.2 months, with a range of 13 to 72 months. Urine output ranged from 300 to 1,000 ml/24 h, and the estimated mean residual GFR ranged from <2 to 5.7 ml/min. Intravenous- and i.p.-administered meropenem was well tolerated; no adverse events were reported during the study period.

The mean and individual concentration-versus-time profiles of meropenem in serum and dialysate over 24 h after i.v. and i.p. administration are shown in Fig. 2 and 3; all calculated meropenem pharmacokinetic parameters are presented in Table 2.

The mean maximum concentrations (C_max) of meropenem in serum were 27.2 mg/liter (SD, ±6.9) and 10.1 mg/liter (SD, ±2.5) and in dialysate were 3.6 mg/liter (SD, ±2.3) and 185.8 mg/liter (SD, ±18.7) after i.v. and i.p. administrations, respectively. After i.v. application, the maximum dialysate concentration was reached after 5.3 h (SD, ±2.2). The maximum serum concentration after i.p. application was observed after 5.7 h (SD, ±0.8).

The mean values for AUC over 24 h (AUC_0–24) of meropenem in serum were 173.5 mg · h/liter (SD, ±29.7) and 141.4 mg · h/liter (SD, ±37.5) (P = 0.046) and in dialysate were 42.6 mg · h/liter (SD, ±20.0) and 623.4 mg · h/liter (SD, ±84.1) (P = 0.028) after i.v. and i.p. administrations, respectively.

The ratios for dialysate exposure over plasma exposure after i.v. and i.p. treatment were 0.2 (SD, ±0.1) and 4.6 (SD, ±0.9), respectively (P = 0.031).

The individual and mean T>MIC values for different MICs are shown in Table 3. A target value of 40% or more of the dosing interval was reached in plasma in all patients after i.v. administration and in five out of six patients after i.p. administration for bacteria with a MIC of ≤4 mg/liter. In dialysate, this target value was easily achieved after i.p. administration for bacteria with a MIC of ≤8 mg/liter. Intravenous administration failed to achieve a sufficient T>MIC for all pathogens with MICs of ≥2 mg/liter.

DISCUSSION

The aim of the present study was to investigate the pharmacokinetics of 0.5 g of meropenem administered i.v. and i.p. in patients with end-stage renal disease on APD therapy. An extensive cycler regimen with 6 cycles in 9 h and a 15-h daytime dwell was chosen to determine drug levels in serum and dialysate over 24 h.

As expected, the half-life of meropenem in serum was prolonged compared to that in patients with intact renal function. The mean half-lives of meropenem in our study were 5.6 (SD, ±1.5) h and 7.6 (SD, ±1.8) h after i.v. and i.p. administrations, respectively. This is slightly below values previously described for patients with end-stage renal disease without renal replacement therapy (11).

At 0.2 and 4.6, a significant difference in the ratios for dialysate exposure and plasma exposure after i.v. and i.p. treatment was observed. While the calculated T>MIC values for exposure to meropenem suggest sufficient antimicrobial effect in serum after i.v. administration as well as i.p. administration, i.v. administration resulted in insufficient i.p. drug exposure (Table 3). These
FIG 2 Mean (± standard deviation) serum and dialysate concentrations of meropenem after intravenous and intraperitoneal administration. The vertical line indicates the start of PD cycles.
FIG 3 Meropenem serum and dialysate concentrations after intravenous and intraperitoneal administration shown for individual patients. Consider the different scales on the y axes. Vertical arrows indicate the start of PD cycles. Pat, patient.
Pharmacokinetics of Meropenem in Peritoneal Dialysis

results are in good agreement with data for other antibiotics, such as fosfomycin, cefotaxime, teicoplanin, vancomycin, and aminoglycosides (3, 12, 13).

Since meropenem demonstrates time-dependent killing, the most important pharmacodynamic index to predict antimicrobial efficacy is the percentage of the dosing interval that the antibiotic concentrations remain above the MIC of the pathogenic organism, and most pharmacodynamic studies have selected a T>MIC of ≥40% of the dosing interval as the target (14). Relevant pathogens for treatment with meropenem, like Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter spp., are listed in the EUCAST breakpoint tables for interpretation of MICs and zone diameters as susceptible with a MIC of ≤2 mg/liter and resistant with a MIC >8 mg/liter (15). According to the data obtained in the present study, i.v. application of 0.5 g of meropenem resulted in adequate serum levels to treat organisms up to a MIC of 4 mg/liter but failed to reach adequate T>MIC values for clinical relevant pathogens in dialysate fluid.

The poor intraperitoneal meropenem exposure after i.v. administration found in the present study is in contrast to former investigations performed with patients not on renal replacement therapy. Karjagin et al. measured meropenem concentrations in peritoneal fluid of septic patients with peritonitis after a dose of 1 g of meropenem i.v. via a microdialysis technique. Meropenem areas under the concentration-time curve in peritoneal fluid reached 73.8% (SD, ±15%) of plasma levels and were thus only slightly lower than in the blood (16). Of interest, the degradation of meropenem ex vivo in the peritoneal fluid was also demonstrated. A recent study performed by our study group, however, demonstrated that meropenem is stable in Extraneal (in contrast to other PD fluids) ex vivo at 37°C (M. Wiesholzer, A. Winter, M. Kussmann, M. Zeitlinger, P. Pichler, H. Burgmann, G. Reznicek, W. Poeppl, submitted for publication).

One possible explanation for the lower i.p. exposure after i.v. administration observed in the present study could be that we examined PD patients without peritonitis. Inflammation of the peritoneum might change permeability for meropenem, resulting in better absorption of the drug but also increased clearance during non-drug-containing dwells. However, Hextall et al. found an i.p. exposure of meropenem of even 95% compared to blood exposure after i.v. administration in 24 patients undergoing elective gastrointestinal surgery for conditions other than infection. They concluded that i.v. meropenem can be used to treat peritonitis. Of interest, high i.p.

### TABLE 2 Pharmacokinetic parameters of meropenem in serum and dialysate after intravenous and intraperitoneal administration of a single dose of 0.5 g of meropenem

<table>
<thead>
<tr>
<th>Sample type</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/liter)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0–24&lt;/sub&gt; (mg · h/liter)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>CL (liters/h)</th>
<th>V (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum after i.p. administration</td>
<td>10.1 ± 2.5</td>
<td>5.7 ± 0.8</td>
<td>141.4 ± 37.5</td>
<td>7.6 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum after i.v. administration</td>
<td>27.2 ± 6.9</td>
<td>0.4 ± 0.3</td>
<td>173.5 ± 29.7</td>
<td>5.6 ± 1.5</td>
<td>2.8 ± 5</td>
<td>22.3 ± 6.9</td>
</tr>
<tr>
<td>Dialysate after i.p. administration</td>
<td>185.8 ± 18.7</td>
<td>0.4 ± 0.3</td>
<td>623.4 ± 84.1</td>
<td>9.3 ± 5.3</td>
<td>0.8 ± 0.1</td>
<td>10.6 ± 6.4</td>
</tr>
<tr>
<td>Dialysate after i.v. administration</td>
<td>3.6 ± 2.3</td>
<td>5.3 ± 2.2</td>
<td>42.6 ± 20</td>
<td>4.1 ± 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are presented as means ± standard deviations. CL, clearance; t<sub>max</sub>, maximum concentration; t<sub>1/2</sub>, half-life; T<sub>max</sub>, time to maximum concentration; AUC<sub>0–24</sub>, area under the curve over 24 h; V, apparent volume of distribution.*

### TABLE 3 Individual, mean, and median percentages of T>MIC values calculated for different MICs

<table>
<thead>
<tr>
<th>Sample type and patient no.</th>
<th>2 mg/liter</th>
<th>4 mg/liter</th>
<th>8 mg/liter</th>
<th>2 mg/liter</th>
<th>4 mg/liter</th>
<th>8 mg/liter</th>
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<td>Serum</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>90.6</td>
<td>66.3</td>
<td>42.0</td>
<td>100.0</td>
<td>91.2</td>
<td>49.8</td>
</tr>
<tr>
<td>2</td>
<td>82.8</td>
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<td>3</td>
<td>70.7</td>
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<td>25.4</td>
<td>56.0</td>
<td>37.6</td>
<td>19.1</td>
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<td>30.2</td>
<td>93.3</td>
<td>59.9</td>
<td>26.5</td>
</tr>
<tr>
<td>5</td>
<td>100.0</td>
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<td>41.9</td>
<td>92.1</td>
<td>62.9</td>
<td>33.7</td>
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<tr>
<td>Mean</td>
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<td>93.5</td>
<td>59.2</td>
<td>25.0</td>
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<td>SD</td>
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<td>34.2</td>
<td>87.3</td>
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<td>10.3</td>
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<td>42.8</td>
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<td>100.0</td>
<td>100.0</td>
<td>88.3</td>
</tr>
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<td>NA</td>
<td>NA</td>
<td>100.0</td>
<td>99.5</td>
<td>75.9</td>
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<tr>
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<td>NA</td>
<td>NA</td>
<td>100.0</td>
<td>96.8</td>
<td>72.7</td>
</tr>
<tr>
<td>4</td>
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<td>10.0</td>
<td>0.0</td>
<td>100.0</td>
<td>100.0</td>
<td>81.2</td>
</tr>
<tr>
<td>5</td>
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<td>100.0</td>
<td>100.0</td>
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</tr>
<tr>
<td>6</td>
<td>26.2</td>
<td>4.4</td>
<td>0.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Mean</td>
<td>31.8</td>
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<td>5.3</td>
<td>100.0</td>
<td>99.4</td>
<td>86.3</td>
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<td>SD</td>
<td>9.5</td>
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<td>11.8</td>
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<tr>
<td>Median</td>
<td>26.4</td>
<td>10.0</td>
<td>0.0</td>
<td>100.0</td>
<td>100.0</td>
<td>84.8</td>
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</table>

*NA, not available.*
exposure after i.v. administration has also been found for other beta-lactam antibiotics (17). Thus, the lower i.p. exposure found in the present study might not just be secondary to the absence of peritoneal inflammation in the patients examined. However, it should be emphasized that in the present study, only patients with chronic PD treatment were included. It was shown that ongoing exposition of the peritoneum to peritoneal dialysis fluid leads to changes of intraperitoneal blood flow and permeability (18). It is noteworthy that one patient enrolled in the present study demonstrated an intraperitoneal C max after i.v. administration of meropenem 3 to 4 times higher than those of the other patients examined.

Comparative to i.v. administration, i.p. application of 0.5 g of meropenem resulted in serum levels adequate to treat organisms up to a MIC of ≤4 mg/liter regarding T>MIC in five out of six patients studied, which suggests a high systemic bioavailability of meropenem after i.p. administration. In dialysate, a target value of 40% or more for T>MIC was achieved even for bacteria with a MIC of 8 mg/liter.

It must be emphasized that in the present study, a single dose of 0.5 g of meropenem was applied, which is in line with the summary of product characteristics for intravenous administration in patients with impaired renal function. However, in clinical practice, higher doses might be applied in patients with renal replacement therapy, which is likely to result in serum concentrations after i.p. administration adequate to treat even less susceptible bacteria.

However, in the literature, pharmacokinetic data for meropenem after i.p. administration are limited to two case reports. Van Ende et al. reported an i.p. application of meropenem in a CAPD patient with systemic bacterial infection: 4 h after the administration of 1 g of meropenem, the serum level was 32 mg/liter, which is approximately three times higher than the mean C max observed in the present study (8). No serial measurements of serum meropenem concentrations and no measurements of dialysate concentrations were performed.

In the other case study, by Vlaar et al., plasma meropenem levels were measured after i.v. and i.p. application of 1 g of meropenem in a patient on CAPD with PD-related peritonitis. The plasma level peaked 4 h after i.p. application. The plasma AUC 0–∞ for i.p. and i.v. administration were 325 and 376 mg · h/liter, respectively, and the estimated bioavailability of i.p. meropenem was 86%. This is in good agreement with the bioavailability of 80.9% obtained in our study in patients without peritonitis. Like in the present study, the AUC 0–∞ and the T>MIC for meropenem during i.p. administration were comparable with those obtained with i.v. administration. Although the patient had significant residual renal function (creatinine clearance of 11 ml/min and urine output of 1 liter/24 h), the serum values of meropenem were above the AUC 0–∞ values measured in patients with regular kidney function treated with 1 g i.v. 3 times a day (7). Again, no measurements of dialysate meropenem levels were performed.

It must also be emphasized that in the present study, only a single dose of meropenem was applied, whereas in the therapeutic setting, the drug will be applied in consecutive intermittent APD day-cycles. However, according to Fig. 2 and 3, only very limited accumulation in the human body would be expected.

In conclusion, the present data suggest that an intermittent dosing regimen with 0.5 g of meropenem i.p. once daily is feasible to treat APD patients with systemic infection caused by pathogens up to a MIC of ≤4 mg/liter. Assuming that the data obtained for noninfected patients can be extrapolated to patients with peritonitis, poor i.p. exposure of meropenem after i.v. application might limit the i.v. use of meropenem for PD-related peritonitis, but i.p. administration would result in an adequate concentration-over-time profile in dialysate as well as in plasma in patients with APD. Our data are in line with current guidelines recommending intraperitoneal administration of antibiotic agents for the treatment of PD-related peritonitis (2, 19).

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