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NOTES

Pharmacokinetics of Meropenem in Critically Ill Patients with Acute Renal Failure Treated by Continuous Hemodiafiltration

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The pharmacokinetics of meropenem were studied in nine anuric critically ill patients treated by continuous venovenous hemodiafiltration. Peak levels after infusion of 1,000 mg over 30 min amounted to 103.2 ± 45.9 μg/ml, and trough levels at 12 h were 9.6 ± 3.8 μg/ml. A dosage of 1,000 mg of meropenem twice a day provides plasma drug levels covering intermediately susceptible microorganisms. Further reductions of the dosage might be appropriate for highly susceptible bacteria or when renal replacement therapies with lower clearances are applied.

Meropenem is a carbapenem antibacterial agent. It is highly active against a broad spectrum of gram-positive and gram-negative bacteria (8) and may be applied as an empirical treatment of severe infections (16, 17). The purpose of this investigation was to study the pharmacokinetics of meropenem in critically ill patients with acute renal failure treated by continuous venovenous hemodiafiltration.

Nine critically ill patients were included in the study after informed consent was obtained by close relatives and after the protocol had been approved by the Ethics Committee of the Eberhard-Karls-Universität, Tübingen, Germany. All patients suffered from acute renal failure with anuria in the course of septic multiple organ failure or due to cardiac failure (Table 1) and were treated by continuous venovenous hemodiafiltration (BSM 22-SC; Hospal, Myezieu, France). A blood flow of 100 ml/min and a countercurrent dialysate flow of 1,600 ml/h were maintained throughout the study period. The dialysate fluid (SH 44-HEP; Schiwa, Glandorf, Germany) was buffered with 8.4% bicarbonate. The hemofilter consisted of AN69 hollow fibers with an effective surface area of 0.90 m^2 (Multiflow 100; Hospal), and the amount of hemodiafiltrate was adjusted as necessary and measured hourly (Table 1). A dose of 1,000 mg of meropenem was administered every 12 h intravenously (i.v.) in 100 ml of 0.9% NaCl through a central venous catheter. Trough levels in plasma were monitored over several days. Blood samples were drawn through an arterial line at 0, 15, 30, 45, 60, 120, 240, 360, and 720 min after the start of a 1,000-mg dose, which was infused over exactly 30 min. Samples of hemodiafiltrate were collected simultaneously with the plasma samples. All blood samples were immediately centrifuged at 693 × *g* for 10 min at 4°C. Aliquots of plasma and diafiltrate were instantly frozen and stored at −80°C. Two to seven days later, levels of meropenem were determined by high-performance liquid chromatography and UV detection by slight modifications of methods described by others (3, 4, 12).

The limit of quantification of meropenem was 0.8 μg/ml in plasma and 2.0 μg/ml in diafiltrate. The response from calibration standards was linear from 1.0 to 100.0 μg/ml for plasma and from 2.0 to 100 μg/ml for diafiltrate. Precision control standards for six different concentrations between 3.0 and 100 μg/ml yielded a relative recovery of 94 to 107%, and the coefficients of variance were 0.6 to 10.3% for plasma and 2.4 to 10.7% for diafiltrate.

Plasma meropenem concentration-time data were analyzed by the trapezoidal method and by linear regression of the terminal phase to determine the area under the concentration-time curve from 0 to 12 h ($AUC_{0–12}$), the clearance, and the elimination half-life. The data were fitted by the pharmacokinetic modelling program MODFIT (1) with a repeated-dose, two-compartment infusion model by weighted least-square regression with weighting as $1/y^2$, and the fit was evaluated from the standard errors of the parameter estimates. The estimated values from the fitted model were used to derive the volume of distribution at steady state and the distribution half-life. The saturation coefficients (S_c) were calculated as $AUC_{0–12}$ values of meropenem in diafiltrate divided by $AUC_{0–12}$ values in plasma. The hemodiafiltration clearance was calculated as $(Q_f + Q_d) \times S_c$, where Q_f is the filtrate flow and Q_d is the dialysate flow (20).

Trough levels of meropenem in plasma were obtained 1 to 7 days after all inclusion criteria had been met and amounted to 9.1 ± 3.2 μg/ml (n = 24; range, 4.7 to 16.3 μg/ml). According to these results, the dosage of 1,000 mg of meropenem twice a day (b.i.d.) was considered appropriate, and the pharmacokinetic investigation was started. Peak levels of meropenem in plasma were reached at the end of the infusion (Fig. 1) and ranged from 67.0 to 205.1 μg/ml (mean, 103.2 ± 45.9). Trough levels at 0 min and after 12 h were 9.4 ± 3.6 μg/ml and 9.6 ± 3.8 μg/ml, respectively (Fig. 1). The saturation coefficient of meropenem was 1.06. Additional pharmacokinetic parameters are listed in Table 1.

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TABLE 1. Demographic and diagnostic information and pharmacokinetic parameters following administration of 1,000 mg of meropenem i.v. for nine anuric critically ill patients treated by continuous hemodiafiltration[a]

Patient no.	Sex[b]	Age (yr)	Weight (kg)	Diagnosis	Infection (APACHE-II scores)[c]	Diafiltrate (liters/h)	$t_{1/2\alpha}$[d] ($t_{1/2\beta}$) (h)	AUC_{0-12} (μg · h/ml)	CL_{total} (CL_{CVVHDF}) (ml/min)	V_{ss}[d] (liters/kg of body wt)
1[e]	F	39	65	Mitral valve endocarditis, respiratory failure, progressive liver failure, pelvic venous thrombosis	Endocarditis, brain abscess (34, 21)	1,850	0.15 (7.38)	287.5	57.98 (31.5)	0.32
2	M	65	66	Thoracoabdominal aortic aneurysm, aortic valve regurgitation, hemorrhage, compartment syndrome of left lower limb	Pneumonia (28, 20)	1,725	0.21 (3.92)	343.1	48.59 (30.0)	0.27
3[e]	F	68	66	Low output syndrome after bivalvular replacement, pulmonary edema	Sepsis[f] (15, 14)	1,875	0.16 (4.51)	295.4	56.43 (33.4)	0.28
4[e]	M	75	76	Coronary bypass, hemorrhage, respiratory failure	Pneumonia[f] (36, 24)	1,650	0.12 (4.75)	354.3	47.05 (29.2)	0.25
5[g]	F	19	65	Polytrauma, subdural hematoma	Pneumonia, sepsis (37, 24)					
6	M	66	91	Myocardial infarctions, mitral valve regurgitation, coronary bypass, postoperative ventricular fibrillation, thrombopenia	Pneumonia[f] (28, 22)	1,725	0.02 (4.82)	539.2	30.92 (30.2)	0.08
7	F	30	56	Cardiomyopathy, respiratory failure, thyreotoxicosis	Pneumonia (14, 20)	1,625	0.21 (2.80)	480.9	34.66 (27.5)	0.17
8	M	65	70	Thoracic aortic aneurysm, hematothorax, respiratory failure	Sepsis[f] (26, 34)	1,850	0.12 (4.54)	250.1	66.65 (32.5)	0.30
9	M	61	70	Cardiopulmonary resuscitation, aortic valve replacement, recurrent ventricular fibrillation	Pneumonia (39, 22)	1,625	0.17 (3.50)	201.6	82.69 (28.9)	0.38
Mean		54.2	69.4		(28.6, 22.3)	1,741	0.15 (4.53)	344.0	53.12 (30.4)	0.26
SD		19.7	9.7		(9.1, 5.3)	105	0.06 (1.35)	114.4	16.83 (2.0)	0.09

[a] $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; AUC_{0-12}, area under the concentration-time curve of plasma meropenem concentrations; CL_{total}, total body clearance of meropenem; CL_{CVVHDF}, clearance of meropenem by continuous venovenous hemodiafiltration; V_{ss}, apparent volume of distribution at steady state.

[b] F, female; M, male.

[c] APACHE-II scores were determined within 24 h of admission to the intensive-care unit and on the day of the pharmacokinetic investigation.

[d] Values derived from fitted biexponential model.

[e] Patient died in intensive-care unit.

[f] Clinical diagnosis could not be proven by microbiological culture.

[g] Patient recovered from renal failure; no pharmacokinetic analysis was done.

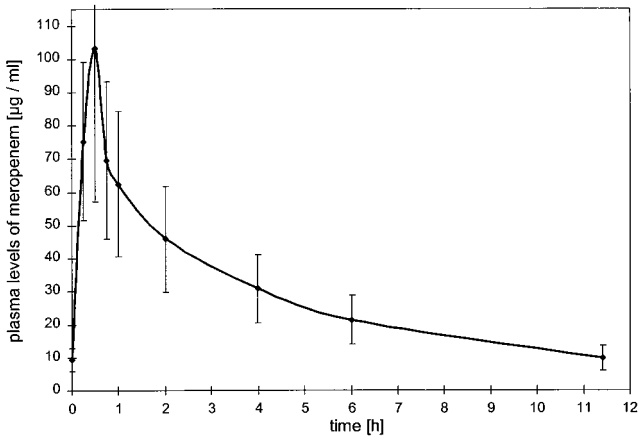

FIG. 1. Levels of meropenem in plasma (means and standard deviations) in eight anuric critically ill patients treated by continuous hemodiafiltration. A dose of 1,000 mg of meropenem was administered as an i.v. infusion over 30 min.

There was no evidence of adverse drug reactions. Three patients died due to cardiocirculatory failure 2, 6, and 18 days after the end of the study, respectively. One patient (patient 5) recovered from renal failure after the third trough level had been determined. No meropenem pharmacokinetic parameters were obtained for this patient.

The elimination half-life of meropenem for our patients was 4.53 ± 1.35 h, which is approximately four times as long as that reported for healthy volunteers (0.8 to 1.2 h) (2, 4, 6, 11, 15, 18). In healthy subjects, meropenem is eliminated by both glomerular filtration and tubular secretion (2). About 62 to 79% of the dose is recovered unchanged in urine, and most of the remainder is also eliminated in urine as the ring-opened metabolite ICI 213,689 (2, 4, 11). In our patients, the hemodiafiltration clearance of meropenem was tightly controlled by the fixed operational characteristics of the renal replacement therapy and amounted to 30.4 ± 2.0 ml/min. This accounted for roughly half of the total body clearance, which had a larger variation and amounted to 54.6 ± 17.0 ml/min. In humans, the 1β-methyl substituent of meropenem confers a high resistance to renal dehydropeptidase I (9), but the β-lactam ring is hydrolyzed in plasma and the relative proportion of this ring-opened metabolite excreted in urine increases with time after administration of the mother compound (11). The high concentrations of circulating metabolite observed in renally impaired subjects suggest that hydrolysis is greater in such patients and that the renal excretion of the metabolite is an important but slow process (5, 6, 15). Thus, it may be assumed that most of the remaining clearance of meropenem in our patients had been accomplished by diafiltration of the metabolite, which is readily dialysable (6, 15).

For patients with normal renal function, meropenem is usually administered every 8 h (3, 17, 19). In end-stage chronic renal failure, the half-life of meropenem is prolonged to 7 to 10 h, so one dose every 24 h is considered appropriate and an additional dose is recommended after dialysis (5, 6, 15). The application interval of 12 h which we had chosen for our patients corresponds well to the recommendations for patients whose creatinine clearances amount to 30 ml/min (5). In such patients, the nonrenal clearance of meropenem contributes to up to 50% of the total body clearance (6), as was the case in our patients.

However, for any dosage recommendations, the operational characteristics of renal replacement therapies as well as physicochemical properties of the drug have to be considered. Only the unbound drug may pass through the hemofilter membrane, which is demonstrated by the close correlation of the unbound fractions of drugs with the corresponding sieving coefficients (10). While sieving refers to the connective transport of drugs along with plasma water in hemofiltration, an additional mechanism of elimination in hemodiafiltration is the diffusion of drugs into the countercurrently flowing dialysis fluid. In this technique, the drug concentration in diafiltrate divided by the concentration in plasma gives the saturation coefficient, which may become smaller with high flow rates that do not allow complete saturation of the dialysis fluid (20). In our study, the saturation coefficient of 1.06 indicates both free passage of meropenem across the filter membrane and enough contact time for complete saturation. This is consistent with the 2% plasma protein binding of meropenem (13), which also largely excludes factors which may influence the hemofiltration of highly protein-bound drugs such as coadministered drugs, bilirubin concentrations, and pH changes (10). There was also no evidence of binding of meropenem to the AN69 filter membrane used in this study nor with polyamide or polysulphone membranes (21). Thus, in the absence of these complicating factors, the clearance of the renal replacement therapy is determined by the amount of filtrate produced and by the dialysate flow rate.

The plasma meropenem concentrations immediately following the infusions were considerably higher in our patients (103.2 ± 45.9 μg/ml) than in healthy volunteers (54.8 ± 6.8 μg/ml) (14, 22). However, these values might not be directly comparable, as we administered meropenem through central venous catheters and drew the blood samples through arterial lines, whereas peripheral veins of opposite arms are used with healthy volunteers. Our approach might have resulted in less distribution of the drug, especially in patients with severe cardiac impairment. However, the antimicrobial effectiveness of β-lactam antibiotics is not enhanced by high peak levels; the most important determinant is the length of time the drug levels remain above the minimal inhibitory concentration (MIC) (7, 23, 24). The mean levels of meropenem in plasma in our study exceeded the MICs for pathogens classified as susceptible or of intermediate susceptibility (MICs of <4 and 8 μg/ml, respectively) (8) throughout the dosing interval (Fig. 1). Indeed, in the case of highly susceptible bacteria, a reduction of the dose might even have been possible.

In conclusion, we consider 1,000 mg of meropenem b.i.d. an appropriate dosage in anuric critically ill patients treated by hemodiafiltration. A lower dosage might be adequate when renal replacement therapies with lower filtrate or dialysate flow are applied or when the MICs for the infecting bacteria are low, so lower trough levels should still be therapeutically effective.

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