ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1992, p. 1532–1537
0066-4804/92/071532-06$02.00/0

Vol. 36, No. 7

Pharmacokinetics of Meropenem in Subjects with Various Degrees of Renal Impairment

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Received 4 November 1991/Accepted 8 May 1992

Five healthy volunteers and 18 patients with various degrees of renal impairment received 500 mg of meropenem intravenously as a 30-min infusion. Five dialysis patients were dosed 2 h prior to hemodialysis, and four of them were also dosed between hemodialysis treatments. Plasma and urine samples were collected for up to 48 h and 12 h, respectively. Concentrations of meropenem and its open ring metabolite ICI 213,689 were determined by high-performance liquid chromatography and radioimmunoassay, respectively. The subjects were divided into four groups with glomerular filtration rates (GFR) of >80, 30 to 80, 5 to 29, or <5 ml/min. There were linear correlations between the GFR and the rates for total plasma clearance as well as renal clearance of meropenem (group mean values for total clearance of 186, 74, 53, and 19 ml/min/1.73 m^2, respectively). In subjects with normal renal function, nonrenal clearance accounted for approximately 20% of total elimination, increasing to about 50% in patients with GFR between 5 and 29 ml/min/1.73 m^2. The terminal half-life of meropenem increased from 0.9 h in the healthy volunteers to 6.8 h in patients with end-stage renal disease. The half-life of ICI 213,689 was 2.31 h in the healthy volunteers and increased to 23.6 h in patients with GFR of 5 to 29 ml/min. In patients with end-stage renal disease, half-lives could not be measured, as concentrations were hardly declining during the 48-h observation period. The area under the concentration-time curve for meropenem increased more than 10-fold. Both meropenem and its open ring metabolite were readily dialyzable, with dialysis clearances of 79 and 81 ml/min/1.73 m^2, respectively.

Meropenem (ICI 194,660) is a new carbapenem antibiotic with high activity against a wide spectrum of pathogenic bacteria (6). It is more stable against renal dehydropeptidase I than imipenem, and there is no need for combination with a dehydropeptidase inhibitor (5). In healthy volunteers, approximately 70% of the compound is excreted unchanged in urine over 12 h (1, 9). Meropenem should be a useful drug for treatment of severe infections. Since many patients who may benefit from this drug will have impaired renal function, a study was undertaken to investigate the influence of renal insufficiency on the pharmacokinetics of meropenem and its open beta-lactam ring metabolite (ICI 213,689).

(This study was presented in part at the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., 21 to 24 October 1990 [abstract 1178].)

TABLE 1. Characteristics of the four groups

Group	No. of subjects (men/women)	Mean (SD)					
		Age and range, yr	Wt, kg	Body surface area, m^2	*S*-Creatinine, μmol/liter	Clearance rate, ml/min/1.73 m^2	
						Iohexol	Creatinine
A	6/0	34 (13.4) 21–58	79 (8.4)	1.96 (0.09)	87 (13.2)	100 (13.4)	99 (22.6)
B	5/0	47 (19.1) 18–68	84 (9.3)	2.02 (0.09	211 (56.2)	37 (5.1)	34 (11.8)
C	5/2	53 (11.2) 35–66	76 (12.4)	1.93 (0.16)	392 (177)	22 (6.8)	17 (8.0)
D	2/3	37 (5.3) 32–45	67 (18.7)	1.77 (0.25)	854 (187)	ND[a]	ND
P[b]		0.06	0.21	0.12	0.0001	0.0001	0.0001

[a] ND, not determined.
[b] *P* calculated as analysis of variance.

MATERIALS AND METHODS

The study protocol was reviewed and approved by the Research Ethics Committee of the Medical Faculty, University of Lund, and by the Swedish Medical Products Agency.

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TABLE 2. Dialysis procedures

Subject no.	Diagnosis	Dialysis equipment	Alwall dialyzer	Blood flow (ml/min)	Dialysate flow (ml/min)	Transmembrane pressure (mm Hg)[a]
19	Chronic pyelonephritis (nephrectomy)	Gambro AK 10	GFE 11	250	500	175
20	Chronic nephrosclerosis, glomerulonephritis	Gambro AK 10	GFE 18	200	500	100
21	Nephropathy of unknown origin	Gambro AK 10-FCM	GFE 15	200	500	100
22	End-stage nephropathy	Gambro AK 10	GFE 18	280	500	95
23	Mesangioproliferative glomerulonephritis	Gambro AK 100	GFE 18	200	500	150

[a] 1 mm Hg = 133.322 Pa.

All participating individuals gave written informed consent before entering the study.

Subjects. Five healthy, male volunteers and 18 patients with various degrees of renal impairment were included in the study. The subjects were divided into subgroups according to renal function as determined by the glomerular filtration rate (GFR) measured as iohexol clearance (8): subjects with GFRs of >80 ml/min/1.73 m^2 (group A, five healthy volunteers and one patient); subjects with GFRs between 30 and 80 ml/min/1.73 m^2 (group B, five patients); subjects with GFRs between 5 and 29 ml/min/1.73 m^2 (group C, seven patients); and subjects with end-stage renal disease (ESRD) being treated with hemodialysis (group D, five patients). Table 1 shows the characteristics of the four study groups. All patients had stable renal function judged by *S*-creatinine measurements for the previous (at least) 6 months. No changes in medication with diuretics or antihypertensives had been made in the 3 months preceding the study.

Laboratory tests. For all subjects, the following laboratory examination was carried out before administration of meropenem and at 24 and 48 to 96 h after dosage: hemoglobin; packed erythrocyte volume; total and differential leukocyte cell count; thrombocyte count; erythrocyte sedimentation rate; serum bilirubin; alanine and aspartate transferase activities; alkaline phosphatase and gamma glutamyltransferase activities; blood glucose; serum sodium, potassium, creatinine, urea, and albumin; and urinalysis (pH, protein, glucose, blood, and microscopy). A determination of the GFR with iohexol clearance measurement was done on the study day on which the iohexol dose was given immediately after the meropenem infusion was stopped, except for subjects in group D for whom no determination of the GFR was performed. Creatinine clearance was calculated with the formulas 88 × (145 − age in years) − 3/serum creatinine concentration in micromoles per liter and 75 × (145 − age in years) − 3/serum creatinine concentration in micromoles per liter for male and female participants, respectively.

Clinical examination. A full clinical examination was done before meropenem was administered. Subjects were given a light breakfast before dosing and were allowed to drink freely but received no food for 3 h after dosing. Coffee, tea, alcoholic beverages, and nicotine in any form were not allowed during the observation period. Blood pressure and pulse frequency were monitored throughout the study day. Subjects were continuously asked, "how do you feel?" before, during, and after dosing, and all observed adverse reactions were noted.

Administration of drug and sampling. Meropenem (500 mg) (ICI Pharmaceuticals, Macclesfield, United Kingdom) was dissolved in 10 ml of sterile water. This solution was further diluted with sterile physiological saline to a total volume of 60 ml at no more than 30 min before start of administration. For each subject, two vials of 500 mg were prepared, the excess solution being used to fill infusion lines and to save an aliquot for drug assay. Each subject received 60 ml of the prepared solution as an intravenous infusion over 30 min through a plastic catheter inserted into a cubital vein. Blood

TABLE 3. Cuprophan hollow-fiber dialyzer performance

Dialyzer	Membrane fiber:		In vitro clearance (ml/min) at perfusion flow of 200 ml/min			Ultrafiltration coefficient (ml/mm Hg/h)
	Thickness (μm)	Inner diameter (μm)	Creatinine	Urea	B_{12}	
Alwall GFE 11	8	200	144	171	52	5.3
Alwall GFE 15	8	200	162	182	62	6.4
Alwall GFE 18	8	200	170	190	70	8.3

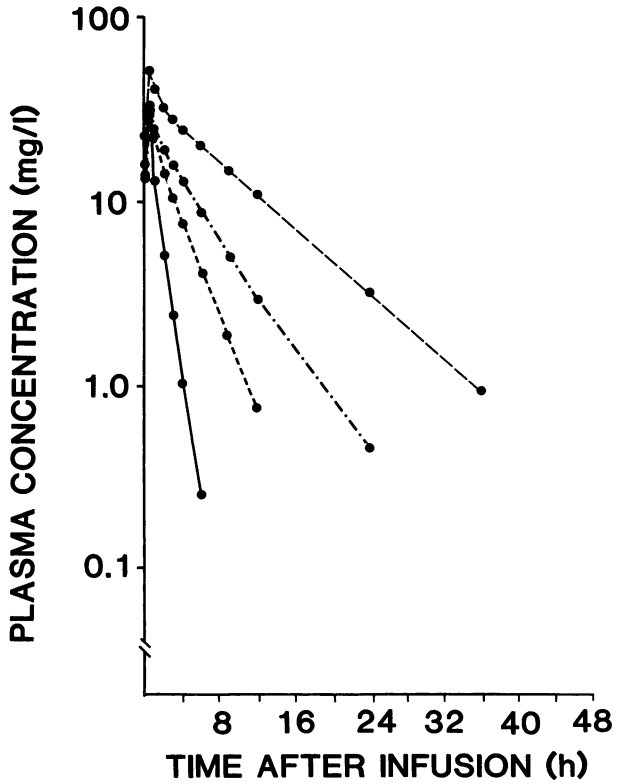

FIG. 1. The mean concentrations of meropenem in plasma for the four different groups: GFR of >80 (——), 30 to 79 (– – –), 5 to 29 (– · – · – ·), and <5 (— —).

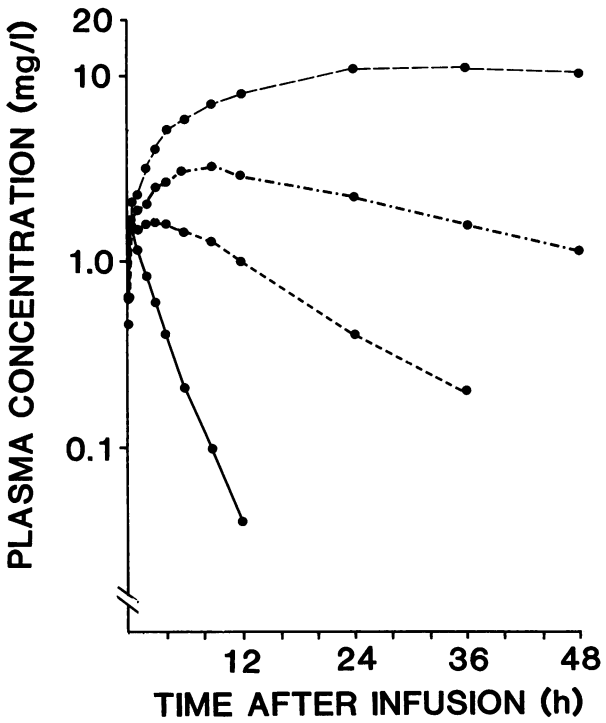

FIG. 2. The mean concentrations of metabolite ICI 213,689 in plasma for the four different groups. Symbols are described in the legend to Fig. 1.

samples were drawn from an intravenous catheter in the contralateral arm before infusion and at 0.17, 0.5, 1, 2, 3, 4, 6, 9, and 12 h after the start of infusion. Additional samples were drawn at 24 and 36 h for group B and at 24, 36, and 48 h for groups C and D when studied between dialyses (all patients with ESRD, except subject 21). Blood samples were kept on ice and centrifuged at +4°C within 30 min. Plasma was divided into two aliquots, instantly frozen in a mixture of ethanol and dry ice, and stored at −70°C until assayed for meropenem and metabolite. Urine was collected quantitatively before infusion and at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, and 10 to 12 h after the start of infusion, except for group D patients who were virtually anuric. The volume of each urine fraction was measured, and two aliquots were instantly frozen in a mixture of ethanol and dry ice and stored at −70°C until assayed.

The effect of hemodialysis on the pharmacokinetics of meropenem was also assessed in group D subjects. Meropenem was prepared and given as described above, with the infusion starting 2 h before hemodialysis. Blood samples were taken before infusion; at 1 and 2 h after the start of infusion; at 0.5, 1, 2, 3, and 4 h after the start of dialysis; and at 1 h after the end of dialysis. The duration of dialysis was 4 h, except for one patient (no. 20) who had 5 h of dialysis. The details of the dialysis procedures are presented in Tables 2 and 3. Blood was taken from both the incoming and the outgoing dialysis lines at each time point during dialysis. Samples were treated and frozen as described above.

Infusion solution aliquots were collected, instantly frozen in a mixture of dry ice and ethanol, and kept at −70°C until assayed.

Statistical analysis. Results were calculated as the group mean with the standard deviation as an estimate of variability. Analysis of variance was used to examine any differences in basic characteristics between the four groups. The individual group variances for pharmacokinetic variables were discordant, making analysis of variance inappropriate. Instead, the Kruskal-Wallis test was used to test differences between the group means. For all statistical analysis, the *P* values are given in the tables.

Assay procedures. Concentrations of meropenem in plasma and urine were assayed at the Department of Infectious Diseases, University of Lund, Lund, Sweden, by high-performance liquid chromatography (2). The limits of detection were 0.4 mg/liter in plasma and 4 mg/liter in urine. The inter- and intra-assay coefficient of variation was less than 6%. Concentrations of the metabolite ICI 213,689 were determined with a radioimmunoassay (2). This assay was undertaken at the Department of Safety of Medicines, ICI Pharmaceuticals. The radioimmunoassay was used over the working range of 40 to 1,000 μg/liter, at which the coefficient of variation was less than 15%.

Pharmacokinetic analysis. Meropenem concentration-time data were analyzed by weighted least-squares regression by using the pharmacokinetic modelling program Siphar software (obtained from SIMED, Creteil, France). The data were fitted to a biexponential infusion model, with weighing of $1/y^2$ from which the rate constants (λ_z) and, hence, terminal half-lives ($t_{1/2}\lambda_z$) were obtained. Other pharmacokinetic variables were calculated by using noncompartmental methods (3) and the original assay concentrations. The renal clearances (CL_R) were calculated by using the ratio of the unchanged drug in urine to the area under the concentration-time curve (AUC) up to 12 h.

TABLE 4. Pharmacokinetic parameters for meropenem for the four groups of volunteers

Group	Mean (SD)									
	C_{max}, mg/liter	$AUC_{0-\infty}$, mg · h/l	λ_z, h −1	$t_{1.2}\lambda_z$, h	MRT[a], h	V_{ss}, liter/kg	CL_T, ml/min/1.73 m²	CL_R, ml/min/1.73 m²	CL_{NR}, ml/min/1.73 m²	U_{REC}, % of dose
A	30.3 (3.6)	36.0 (4.5)	0.769 (0.140)	0.93	1.24 (0.19)	0.21 (0.03)	186 (28)	142 (26)	44 (25)	77 (12)
B	31.7 (5.1)	89.8 (17.9)	0.304 (0.053)	2.34	3.27 (0.75)	0.20 (0.02)	74 (16)	41[c] (16)	35[3] (9)	53[3] (12)
C	33.1 (5.8)	156 (63.8)	0.199 (0.057)	3.82	5.37 (1.89)	0.23 (0.03)	53 (16)	23 (12)	29 (4)	38 (14)
D[b]	53.1 (10.9)	393 (83.8)	0.102 (0.009)	6.81	9.36 (0.67)	0.17 (0.02)	19 (2)			
P	0.020	0.0003	0.0003		0.0004	0.025	0.004	0.002	0.28	0.005

[a] MRT, mean residence time.
[b] Only four individuals were included; one patient with ESRD did not participate in the between-dialyses study.
[c] One individual was excluded because of incomplete urine collection.

TABLE 5. Pharmacokinetic parameters for the metabolite ICI 213,689

Group	Mean (SD)					
	C_{max}, mg/liter	T_{max}, h	$t_{1/2}\lambda_z$, h	$AUC_{0-\infty}$, mg · h/liter	U_{REC}[a], % of dose	
					Metabolite	Meropenem + metabolite
A	1.51 (0.29)	0.58 (0.20)	2.31	4.63 (1.41)	22 (6)	99
B	1.89 (0.18)	3.60 (3.49)	9.11	31.0 (13.7)	13[b] (5)	65[b]
C	3.46 (1.33)	7.44 (2.69)	23.6	1.68 (163)	6 (3)	44
D[c]	11.7 (2.36)	33.0 (11.5)	NC[d]	405[e] (57.7)		
P	0.005	0.001	0.0005	0.0003	0.003	0.002

[a] U_{REC}, urinary recovery for 0 to 12 h; corrected for molecular weight differences.
[b] One individual was excluded because of incomplete urine collection.
[c] Only four individuals were included; one patient with ESRD did not participate in the between-dialyses study.
[d] NC, not calculated.
[e] AUC for 0 to 48 h.

The plasma metabolite concentration-time data were inspected visually, and those points constituting a terminal phase were subjected to log-linear regression to determine the terminal half-lives. Metabolite data were analyzed by using noncompartmental model methods (3).

The clearances of meropenem and its metabolite during hemofiltration were calculated as $CL_D = [(C_A - C_V)/C_A] \times (1 - H) \times BF$, where CL_D is the clearance during dialysis; C_A and C_V are the concentrations of drug in outgoing and incoming lines, respectively; H is the hematocrite as a fraction of 1; and BF is the blood flow through the dialyzer.

RESULTS

Meropenem was well tolerated in all subjects. No adverse reactions were reported. The physical and laboratory examinations before, during, and after the study revealed no changes related to the drug.

The group mean plasma concentration-time curves of meropenem and its metabolite ICI 213,689 are shown in Fig. 1 and 2. A decreasing elimination rate of both parent compound and metabolite in patients with renal impairment was seen. The mean pharmacokinetic parameters of meropenem and its metabolite derived from the concentrations in plasma and urine are given in Tables 4 and 5, respectively. In the mixed group of subjects with both male and female patients and volunteers, the body surface area varied from 1.61 to 2.17 m^2. Hence, clearances except dialysis clearances were calculated per 1.73 m^2 of body surface area. For the same reason, the volume of distribution at steady state (V_{ss}) was given as liters per kilogram of body weight. Total clearance (CL_T) of meropenem and GFR were linearly correlated ($y = 1.71x + 14.0$, $r = 0.981$) (Fig. 3). Likewise, renal clearance (CL_R) of meropenem showed linear correlation with GFR ($y = 1.52x - 11.7$, $r = 0.974$) (Fig. 4). Since urine was collected for 12 h only, data on urinary recovery (U_{REC}), especially for groups B and C, did not reflect complete urinary excretion. This was true for meropenem and, to an even larger degree, for its metabolite ICI 213,689, of which substantial amounts persisted in the circulation of renally impaired subjects after 12 h. Since metabolism was going on throughout the study period, the terminal half-life ($t_{1/2}$) calculated should be considered an estimate, not a true elimination half-life. Meropenem was readily dialyzed, as can be seen from the mean plasma data obtained during dialysis (Fig. 5), as was the metabolite. The CL_D for meropenem and the metabolite were 79 ml/min (standard deviation, 10.4) and 81 ml/min (standard deviation, 17.7), respectively.

DISCUSSION

Our pharmacokinetic results for healthy volunteers correlate well with those published earlier (1, 2, 5, 6, 9). With decreasing GFR, no changes in the volumes of distribution (V_{ss}) were noted. The increase in maximum concentration of drug (C_{max}) in plasma seen in patients with ESRD is mainly explained by the lack of renal elimination, as differences in V_{ss} were not observed. In healthy volunteers, meropenem is mainly eliminated by the kidneys (1, 2, 9). In our healthy volunteers, CL_R of meropenem exceeded the GFR, indicating that renal excretion is both by glomerular filtration and by tubular secretion. With progressive renal failure, CL_R of meropenem decreased and the nonrenal pathway of elimination became relatively more important, increasing from 20% of CL_T for group A to about 50% for group C. The main mechanism for nonrenal elimination of carbapenems is metabolism (11). For imipenem, metabolism by dehydropepti-

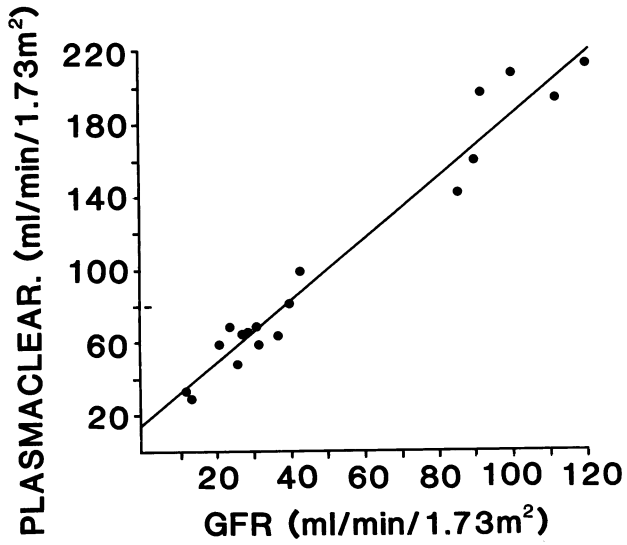

FIG. 3. The relationship between plasma clearance of meropenem and GFR for 18 subjects.

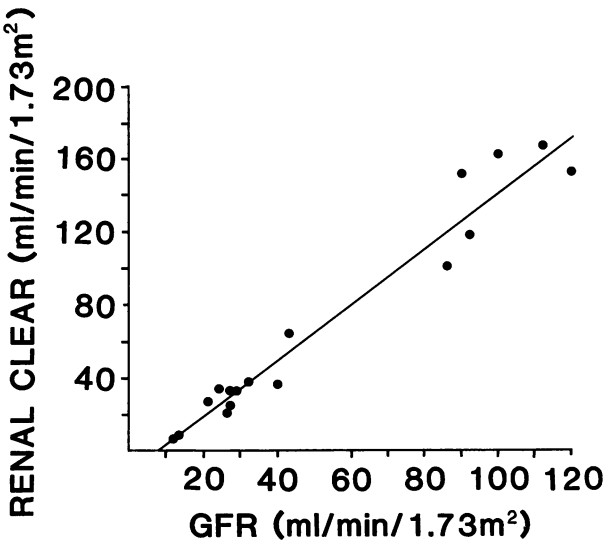

FIG. 4. The relationship between renal clearance of meropenem and GFR for 18 subjects.

dase I in the brush border of the proximal renal tubule has been demonstrated previously (7), and the population seems to be bimodally distributed in high and low metabolizers (10). Subjects who are high metabolizers of imipenem seem also to metabolize meropenem more rapidly than low metabolizers, but since meropenem is considerably more stable to dehydropeptidase I at least 65% of the dose is excreted unchanged in the urine (2). Imipenem undergoes nonrenal metabolism or degradation as indicated by an increasingly higher clearance of imipenem compared with that of cilastatin in patients with renal insufficiency (4). The plasma clearance data for group D represent nonrenal clearances since these patients have virtually no renal clearance. Especially in subject 19, who has undergone bilateral nephrectomy, all clearance from plasma must have been nonrenal. The results for this patient clearly showed that there was extrarenal metabolism or degradation of meropenem; the metabolite concentrations measured in this patient's plasma samples must be of extrarenal origin. The other four patients in group D had plasma metabolite concentrations and AUCs in the same range as those of patient 19, and it can be assumed that the renal metabolism of meropenem diminishes as renal function deteriorates. No elimination kinetics of ICI 213,689 were established, since the observation period was too short.

Our way of calculating dialysis clearance is based on the assumption that meropenem and its metabolite are not bound to erythrocytes and, as no collection of dialysate fluid was done, might give underestimated values as the water efflux through the dialysis membrane is not accounted for.

As with other neurotoxic beta-lactam antibiotics, imipenem combined with cilastatin appears to evoke seizures by blocking gamma aminobutyric acid receptors (14, 16). Animal experiments show that the concentrations of beta-lactam in brain tissue are better correlated to neurotoxic effects than are the concentrations measured in cerebrospinal fluid (13). In different studies, both imipenem (6) and its open ring metabolite (15) have been implicated. If metabolite concentrations are involved in the mechanism for initiating seizures, meropenem with its lesser degree of metabolism should constitute a smaller risk for severe central nervous system adverse effects. However, in our patients with ESRD, high concentrations of metabolite persisted between dialyses and no untoward effects were observed. So far, one study of mice has shown that meropenem has less potential for causing seizures than does imipenem (12).

Judging from the results of this investigation, it seems logical to base dosing recommendations on renal function as there is excellent linearity between the GFR and CL_T of meropenem. As seen in Table 1, the differences in calculated creatinine clearance and measured GFR were not great, and our dosing recommendations might also be used with creatinine clearances. A proposed dosing schedule is presented in Table 6. However, since all our data are based on this

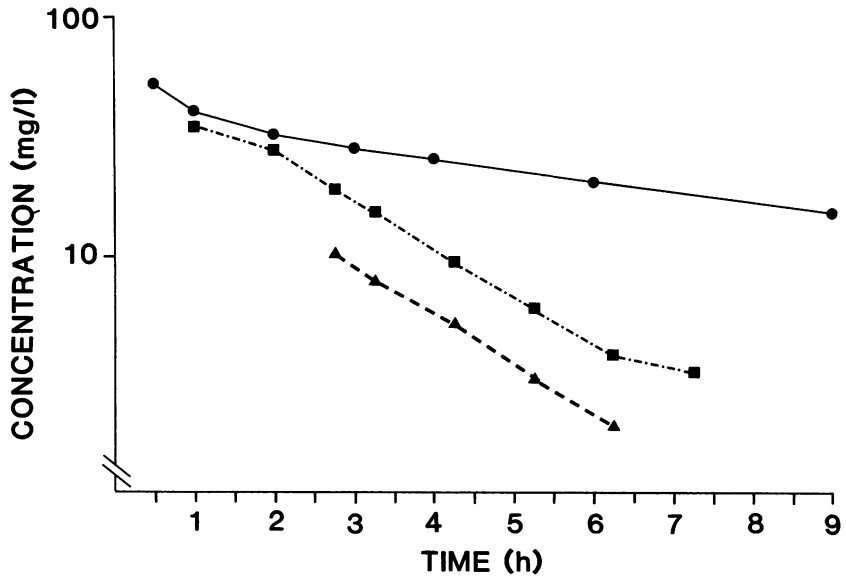

FIG. 5. The mean concentrations of meropenem in plasma for group D patients between dialysis (——) and during dialysis. During dialysis, samples were taken from blood lines entering (– · – · –) and leaving (– – –) the dialyzer.

TABLE 6. Dosing recommendations for patients with renal impairment

GFR (ml/min)	Dose (mg)	Dose interval (h)
>50	500–1,000	6–8
26–50	500–1,000	12
0–25	250–500	12
<10	250–500	24[a]

[a] Additional dose after hemodialysis.

single-dose study, they should be considered recommendations for further controlled multiple-dose studies to determine the degree of accumulation of parent compound and metabolite and not be used in immediate clinical practice. However, both metabolite and parent compound are readily dialyzable, and an additional dose of meropenem is recommended after hemodialysis.

ACKNOWLEDGMENTS

Financial support was given by ICI Pharmaceuticals, Macclesfield, United Kingdom, and by the Medical Faculty, University of Lund, Lund, Sweden.

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