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Pharmacokinetics of Meropenem in Patients with Various Degrees of Renal Function, Including Patients with End-Stage Renal Disease

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The pharmacokinetics of meropenem were studied after intravenous infusion in 13 patients grouped according to the impairment of their renal function. Creatinine clearance (CL_{CR}) was greater than 50, 50 to 30, and less than 30 ml/min in groups I, II, and III, respectively. Two other groups, groups IV and V, each comprising four patients with end-stage renal disease (CL_{CR}, <5 ml/min), were also studied, the former on days off of hemodialysis and the latter on days of hemodialysis. The elimination half-lives of meropenem were 1.54 ± 0.70 h in group I patients, 3.36 ± 1.02 h in group II patients, and 5.00 ± 1.05 h in group III patients. Cumulative urinary excretion accounted for 48.5% of the dose in group I patients and decreased progressively with a decline in renal function. Hemodialysis shortened the elimination half-life of meropenem from 7.0 h to 2.9 h. H-4295, the main metabolite of meropenem, had a peak level in plasma of 0.5 to 1.0 h in patients with renal failure. The level of H-4295 decreased with hemodialysis. The dosing interval of meropenem should be prolonged in a regular proportion to the decline in CL_{CR} (12 h in group II patients and 24 h in group III patients). In patients receiving hemodialysis, dosing after each hemodialysis session is recommended.

Meropenem is a new carbapenem antibiotic with a broad spectrum of in vitro activity against both gram-positive and gram-negative bacteria (4) and is more potent than imipenem in vitro against members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (2). Meropenem has also exhibited excellent in vitro results against bacteria that produce a variety of β-lactamases (8). Imipenem is easily degraded by dehydropeptidase I (DHP-I), a zinc metalloenzyme that resides in the brush border or within tubular cells (12). Thus, since extensive metabolism of imipenem results in the recovery of small amounts of intact, microbiologically active, antibiotic, it therefore requires coadministration of the DHP-I inhibitor cilastatin. Cilastatin also contributes to the elimination of the nephrotoxic potential of imipenem by preventing tubular injury induced by a high dose (>100 mg/kg of body weight) of antibiotics in rabbits (7). In contrast, since meropenem is stable to DHP-I, the drug has a lower potential for nephrotoxicity than imipenem (11) and does not require the administration of a DHP inhibitor. However, since studies in healthy volunteers have shown that meropenem is eliminated primarily unchanged in the urine (1), accumulation of meropenem is likely to occur in patients with reduced renal function.

The investigation described here was thus undertaken to elucidate the pharmacokinetic disposition of meropenem in patients with various degrees of renal impairment and to determine the extent of extraction of meropenem during hemodialysis.

MATERIALS AND METHODS

Thirteen patients (five men, eight women) with various degrees of renal impairment gave their informed consent and were entered into the study. A complete medical history, a physical examination, and a laboratory profile were obtained for each subject before and after the study period. The subjects received no other antibiotics during the study, and all other medications were administered as prescribed by the subjects' physicians.

The patients were then separated into three groups according to the following endogenous creatinine clearance (CL_{CR}) values: $CL_{CR} \geq 50$ ml/min (group I), CL_{CR} = 50 to 30 ml/min (group II), and $CL_{CR} \leq 30$ ml/min (group III). CL_{CR} was used as an index for the glomerular filtration rate and was determined by measuring CL_{CR} over 24 h. Eight additional anuric patients with end-stage renal disease were further divided into groups IV and V, each consisting of four patients. The patients in groups IV and V were subjected to the study on their days off and on hemodialysis, respectively.

Meropenem was administered to group I, II, III, and IV patients at a dose of 500 mg dissolved in 100 ml of 5% glucose solution and was infused over a 30-min period. Heparinized blood samples (5 ml) were collected before drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after the start of the infusion. Urine samples (when available) were collected at 0 to 6 and 6 to 12 h from patients in groups I and II and at 0 to 6, 6 to 12, and 12 to 24 h from patients in group III. Blood samples were immediately placed on ice and centrifuged. Samples were kept frozen at −70°C until assayed. The sex, age, weight, and estimated CL_{CR} of all subjects are listed in Table 1.

For group V patients undergoing regular hemodialysis, a single dose of 500 mg was given for a period of 30 min and hemodialysis was initiated at the completion of the infusion. Hemodialysis was then performed for 4 h with DBB-22 dialyzer units (Nikkiso Co.) with single-pass dialysate flow and hollow-fiber cuprophane membrane artificial kidneys. Blood flow was maintained at a constant rate and was measured for each subject by bubble transit time. Rates of dialysate flow were determined by collecting and measuring total hourly dialysate volumes. Total membrane pressure

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TABLE 1. Subject characteristics

Group	Subject no.	Age	Sex[a]	Wt (kg)	Serum creatinine concn (mg/dl)	CL_{CR} (ml/min)
I	1	55	F	40	0.5	68.0
	2	68	F	34	0.8	62.5
	3	49	F	43	0.8	57.3
	4	30	F	62	1.1	55.7
II	5	61	M	85	1.6	37.3
	6	48	M	65	2.2	34.5
	7	48	M	66	1.8	32.7
	8	60	F	43	1.3	32.0
III	9	66	M	52	4.0	21.5
	10	46	F	58	2.7	16.2
	11	61	F	58	5.3	11.3
	12	76	M	52	4.2	7.1
	13	74	F	50	7.0	4.3
IV	14	63	F	31	10.9	—[b]
	15	53	F	58	12.6	—
	16	41	F	51	10.9	—
	17	61	F	40	10.5	—
V	18	77	F	39	8.7	—
	19	57	M	52	13.9	—
	20	44	M	59	11.1	—
	21	48	F	42	9.9	—

[a] F, female; M, male.
[b] —, CL_{CR} < 5 ml/min.

was recorded, and negative membrane pressure was minimized to prevent excessive ultrafiltration. Blood samples were collected from the arterial and venous tubes during hemodialysis. Samples were then centrifuged, and plasma was immediately harvested and was frozen until it was assayed. The hemodialysis characteristics are listed in Table 2. Blood samples were collected before administration of the dose and at 0.5, 1, 2, 3, 4, 6, 8, and 12 h thereafter.

Analytical method. The meropenem concentrations in plasma, urine, and dialysate samples were assayed microbiologically by using the thin-layer paper disc method performed in Mitsubishi Yuka Bio-Clinical Laboratories, Inc., Tokyo, Japan. For the bioassay, *Escherichia coli* NIHJ grown in nutrient agar was used as the test organism. Plasma and urine samples were diluted with 0.05 M 3-*N*-morpholinopropanesulfonic acid buffer (pH 7.0). The correlation of the regression line was $r = 0.9967$. The lowest detectable concentrations in plasma and urine were 0.06 μg/ml.

Plasma and urine samples were assayed for H-4295, the open-lactam metabolite of meropenem, by a high-pressure liquid chromatographic (HPLC) assay performed at the Sumika Chemical Analysis Center Co. Ltd., Osaka, Japan. The HPLC assay was performed with a Cosmosil SC18 column and an Hitachi model L-6000, L-6200, and L-4000 fixed-wavelength spectrophotometer set at an A_{215}. The mobile phase consisted of 80% (vol/vol) 5 mM tetrabutylammonium dihydrogen phosphate solution and 20% (vol/vol) methanol. The flow rate was 1 ml/min. The correlation of the regression line and coefficients of variation were 0.9987 and 1.1%, respectively, for plasma and 0.9992 and 6.1%, respectively, for urine. The lowest detectable concentration in plasma was 0.5 μg/ml, and the lowest detectable concentration in urine was 10 μg/ml.

TABLE 2. Hemodialysis characteristics[a]

Subject no.	Surface area of dialyzer membrane (m^2)	Ht (%)[b]	Blood flow (ml/min)[c]
18	1.0	25.7	180
19	1.5	21.7	230
20	1.5	25.7	200
21	1.0	22.3	180

[a] Dialysate flow was 500 ml/min for all subjects; it was measured from total hourly dialysate collections.
[b] Ht, hematocrit value from predialysis samples.
[c] Blood flow, measured by bubble transit time.

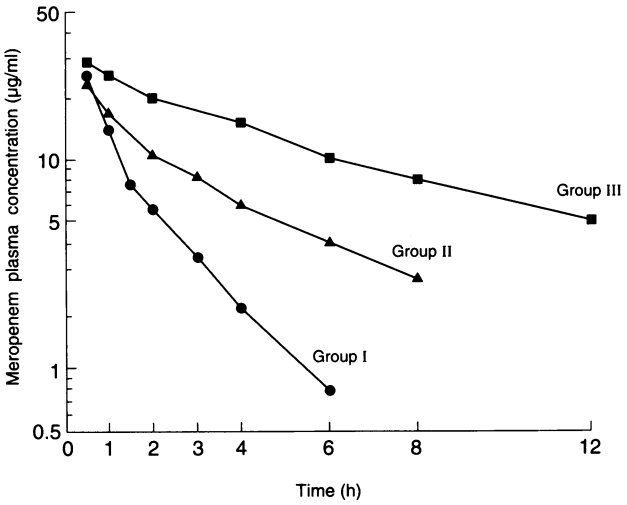

FIG. 1. Plasma meropenem concentration-time curve in subjects with various renal functions.

Pharmacokinetic analysis. A two-compartment model with constant-rate input was used to describe the drug concentration in plasma. The pharmacokinetic parameters were estimated by nonlinear least-squares regression (13). The half-life was calculated by dividing the terminal elimination rate constant estimated from the pharmacokinetic model into the natural logarithm of 2 (13). The estimate of meropenem clearance (CL) from plasma was determined by using the noncompartment equations $CL = \text{dose}/AUC_{0-\infty}$, where $AUC_{0-\infty}$ is the area under the plasma concentration-time curve from time zero to infinity.

Renal clearance (CL_R) was calculated by the equation $CL_R = A_e/AUC_{0-\infty}$, where A_e is the total amount of meropenem recovered in the urine over time.

RESULTS

In the 13 subjects with various degrees of impaired renal function, the peak meropenem concentrations achieved immediately after infusion of 500 mg given over 30 min ranged from 9.9 to 45.2 μg/ml. Plasma concentration-time curves representative of subjects in groups I, II, and III are shown in Fig. 1. Plasma meropenem levels declined in a biexponential fashion. The terminal half-life increased and the CL_R decreased with decreasing renal function. The ratios of CL_R and CL_{CR} ranged from 0.28 to 3.88 (Table 3).

A significant correlation was found between meropenem clearance from plasma and CL_{CR} ($P < 0.0001$) (Fig. 2).

TABLE 3. Meropenem pharmacokinetic data[a]

Group	Subject no.	$t_{1/2}$ (h)	AUC (μg · h/ml)	CL (ml/min)	CL_R (ml/min)	CL_R/CL_{CR} ratio
I	1	1.71	24.0	347.2	263.9	3.88
	2	0.61	50.7	164.4	73.6	1.18
	3	2.31	35.8	232.8	74.3	1.30
	4	1.54	36.0	231.5	95.4	1.71
Mean ± SD		1.54 ± 0.70	36.6 ± 11.9	244.0 ± 75.9	126.8 ± 92.0	2.02 ± 1.26
II	5	4.45	40.2	207.3	80.0	2.14
	6	4.01	88.5	94.2	26.6	0.77
	7	2.46	63.3	131.6	66.7	1.76
	8	2.53	106.5	78.2	11.9	0.28
Mean ± SD		3.36 ± 1.02	74.6 ± 29.0	127.8 ± 57.5	46.3 ± 32.3	1.24 ± 0.86
III	9	4.52	112.2	74.3	32.2	1.50
	10	3.58	136.3	61.1	21.9	1.35
	11	5.69	173.1	48.1	9.5	0.84
	12	4.94	235.6	35.4	5.8	0.82
	13	6.29	276.6	30.1	7.5	1.74
Mean ± SD		5.00 ± 1.05	186.8 ± 68.5	49.8 ± 18.2	15.4 ± 11.3	1.25 ± 0.41

[a] $t_{1/2}$, half-life; AUC, area under the concentration-time curve; CL, meropenem clearance from plasma; CL_R, renal clearance; CL_{CR}, creatinine clearance.

Concentrations of meropenem in the urine of subjects in group I were 203 to 424 μg/ml for the first 6 h after the dose was administered and 52 to 383 μg/ml at 6 to 12 h; and subjects in group II had levels of 118 to 484 μg/ml for up to 6 h and 10 to 120 μg/ml for 6 to 12 h. Patients in group III had levels of 209 to 289 μg/ml for up to 6 h, 52 to 240 μg/ml for 6 to 12 h, and 18 to 156 μg/ml for 12 to 24 h.

The concentration-time curves of H-4295 with decreased CL_{CR} are shown in Fig. 3. The H-4295 level increased with decreasing renal function.

The concentrations of H-4295 in the urine of subjects in group I were 32 to 174 μg/ml for the first 6 h after administration and 19 to 252 μg/ml for 6 to 12 h; those for group II subjects were 24 to 91 μg/ml for up to 6 h and 39 to 83 μg/ml for 6 to 12 h. Patients in group III had levels of 21 to 105 μg/ml for up to 6 h, 19 to 96 μg/ml for 6 to 12 h, and 10 to 74 μg/ml for 12 to 24 h.

The cumulative recovery rates of meropenem and H-4295 in urine were 37.3 to 88.2%, 21.5 to 62.2%, and 20.1 to 54.3% of the administered dose for 0 to 12 h in groups I, II, and III, respectively (Table 4).

The concentrations of meropenem in the plasma of the eight subjects on hemodialysis are shown in Fig. 4.

The concentration-time curves of H-4295 for subjects on hemodialysis are shown in Fig. 5. The H-4295 level decreased during hemodialysis.

DISCUSSION

The study of the pharmacokinetic disposition of meropenem in normal subjects has shown a maximum concentration in plasma of 26.0 ± 3.9 μg/ml and an elimination half-life of 1.03 ± 0.13 h after administration of a dose of 500 mg (6).

Meropenem is mainly excreted via the renal route. Indeed, more than 64% of the administered meropenem is excreted in the urine (1). As Bax et al. (1) have reported, 30 to 40% of

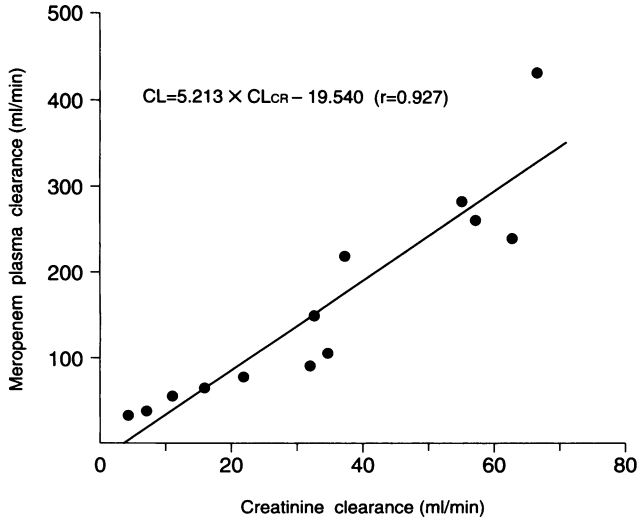

FIG. 2. Correlation between CL_{CR} and meropenem clearance from plasma.

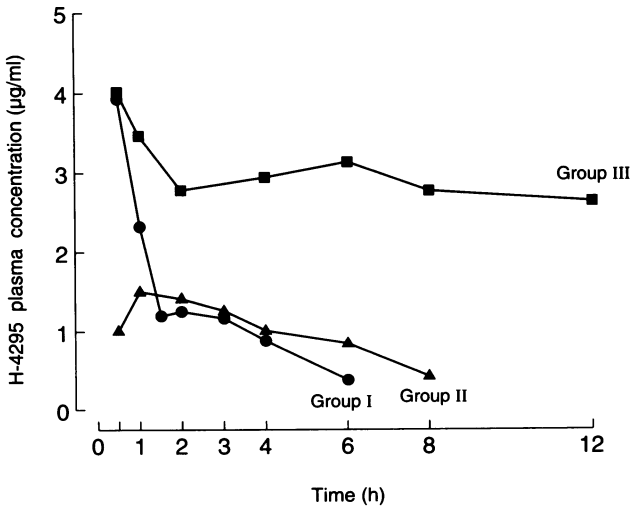

FIG. 3. Concentration of H-4295 in the plasma of subjects with various renal functions.

TABLE 4. Recovery rate of meropenem and H-4295 in urine

Group	Subject no.	Recovery rate (%) in urine		
		Meropenem	H-4295	Total
I	1	76.0	12.2	88.2
	2	44.8	8.7	53.5
	3	31.9	5.4	37.3
	4	41.2	22.3	63.5
Mean ± SD		48.5 ± 19.1	12.2 ± 7.3	60.6 ± 21.3
II	5	38.6	14.0	52.6
	6	28.2	22.8	51.0
	7	50.7	11.5	62.2
	8	15.2	6.3	21.5
Mean ± SD		33.2 ± 15.1	13.7 ± 6.9	46.8 ± 17.6
III	9	43.3	11.0	54.3
	10	35.9	14.5	50.4
	11	19.8	8.8	28.6
	12	16.3	3.8	20.1
	13	24.8	3.2	28.0
Mean ± SD		28.0 ± 11.3	8.7 ± 4.8	36.3 ± 15.1

the meropenem excreted in urine comes from tubular excretion and the remainder comes from glomerular filtration. The results of the present study are consistent with those of Bax et al. (1), in that CL_R significantly correlated with CL_{CR}. However, it remains to be explored whether the converse is true, that is, whether meropenem influences the tubular handling of other drugs.

Clinical trials have demonstrated that a dosage regimen of 500 mg given twice daily is effective in the management of urinary tract infections (5). In fact, in Europe and the United States, the dosing interval for normal patients has been every 6 or 8 h. The MICs of meropenem for 90% of most pathogens tested are less than 0.1 to 0.2 μg/ml except for coagulase-negative staphylococci and *P. aeruginosa* (9). Meropenem still exhibits significant postantibiotic effects against the majority of gram-negative organisms, gram-positive aerobes, and *Bacteroides fragilis* with the concentrations obtained after dosing every 8 to 12 h (10). Therefore, our dosing regimen could be effective in patients with normal renal function. However, from the results of our study, we recommend that the dosing intervals be prolonged in proportion to the decrease in the glomerular filtration rate in patients with renal disease.

Our study also showed the accumulation of meropenem in subjects with reduced renal function and off of hemodialysis. Although the toxicity of the metabolite of meropenem in animals was less toxic compared with that of imipenem, the clinical significance of the metabolites in humans is not yet well known.

From this viewpoint, therefore, we recommend that the dosing intervals be prolonged to 12 h (for subjects with a CL_{CR} of 30 to 50 ml/min) and 24 h (for subjects with a CL_{CR} of <30 ml/min) to avoid unnecessary accumulation of meropenem and/or its metabolites to minimize the risk of side effects. The recommended dosage intervals for patients with renal failure characterized as CL_{CR} values of ≥50, 50 to 30, and ≤30 ml/min are 8 to 12, 12, and 24 h, respectively.

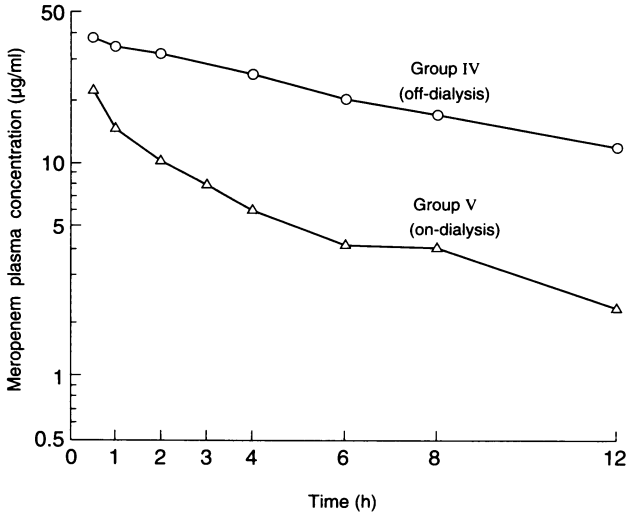

FIG. 4. Plasma meropenem concentration-time curve in patients on hemodialysis.

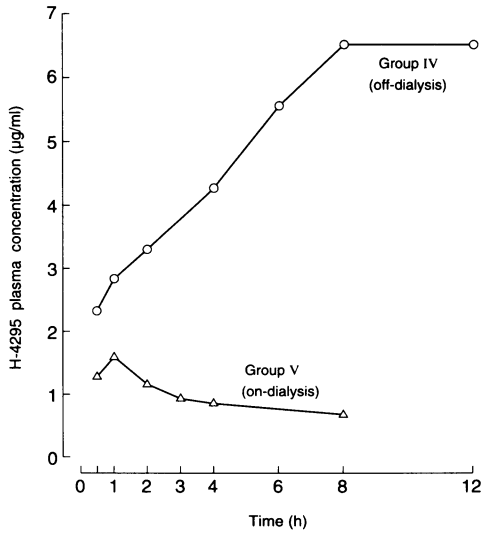

FIG. 5. H-4295 concentration in subjects on hemodialysis.

The elimination half-life of meropenem is 2.9 h in patients receiving hemodialysis and is prolonged to about 7.0 h in patients with end-stage renal disease but not receiving hemodialysis. The amount of drug eliminated by hemodialysis depends on the surface area of the dialysis membrane, blood flow, and the duration of hemodialysis. However, since little meropenem is bound to plasma protein in the circulation (3), a considerable amount is removed during hemodialysis, as shown in Fig. 4, resulting in the requirement of supplemental dosing after each hemodialysis session.

In patients under regular hemodialysis, dosing of 500 mg at the end of each dialysis two to three times a week is recommended.

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