Pharmacokinetics of Meropenem (ICI 194,660) and Its Metabolite (ICI 213,689) in Healthy Subjects and in Patients with Renal Impairment

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The pharmacokinetics of meropenem (ICI 194,660) and its open-ring metabolite (ICI 213,689) were studied in 6 healthy volunteers and 16 patients with moderate to severe renal impairment after a single intravenous dose of 500 mg given as a 30-min infusion. Concentrations of unchanged meropenem in plasma and urine were measured by both microbiological and high-pressure liquid chromatographic (HPLC) assays. A good correlation was found between the two techniques. Pharmacokinetic parameters of unchanged meropenem were determined by using the HPLC data. The terminal half-life of unchanged meropenem increased in relation to the degree of renal impairment, being 1.2 h in subjects with normal renal function and 10 h in patients with end-stage renal failure. Total body clearance and renal clearance of unchanged meropenem are linearly related to creatinine clearance. The concentrations of the metabolite in plasma, which are very low in healthy subjects, significantly increased in uremic patients. The apparent half-life of ICI 213,689 increased in uremic patients and was about 35 h in patients with severe renal insufficiency. Meropenem and its metabolite are effectively removed by hemodialysis. The dialysis clearance of the unchanged drug was 81 ± 22 ml/min. Dosage adjustments of meropenem will be necessary in patients with severe renal impairment.

Meropenem (ICI 194,660) is a new parenteral carbapenem antibiotic characterized by a broad antibacterial spectrum. It has been shown to have activity against both gram-positive and gram-negative pathogens, including anaerobes such as *Bacteroides fragilis*. Meropenem is more active in vitro than imipenem against members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Unlike imipenem, meropenem shows a good stability against human renal dehydropeptidase I and does not require the coadministration of a dehydropeptidase I enzyme inhibitor such as cilastatin (4, 7, 9–11).

The purpose of this study was to investigate the pharmacokinetics of meropenem (ICI 194,660) and of its open-ring metabolite (ICI 213,689) in patients with moderate or severe renal impairment after a single intravenous (i.v.) dose of 500 mg given as a 30-min infusion.

(This study was presented in part at the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy in Chicago, Ill. [8a].)

MATERIALS AND METHODS

Subjects. Twenty-two subjects with no known problems with antibiotics participated in the study after Ethical Committee approval and written informed consent had been obtained. The characteristics of the subjects are given in Table 1.

Six adult volunteers aged from 23 to 48 years and weighing from 51 to 88 kg were selected for the study as a control group. These subjects had no evidence of hepatic, hematological, or renal disease confirmed by physical examination and hemobiological and biochemical tests. Their renal

functions were healthy, with a mean creatinine clearance (CL_{CR}) of 122 ml/min.

Sixteen subjects had chronic renal impairment with stable CL_{CR}s during the previous 6 months. The subjects were divided into three groups on the basis of glomerular filtration rate as determined by CL_{CR}: group 1 (moderate renal impairment; $n = 6$), 12 to 23 ml/min; group 2 (severe renal impairment; $n = 4$), 4 to 8 ml/min; and group 3 (hemodialysis patients; $n = 6$). CL_{CR} was measured during the first 24 h of the study by determination of creatinine concentrations in plasma and urine by using the formula CL_{CR} (ml/min) = {[urine (μmol/liter)] × V (ml/min)}/[plasma (μmol/liter)], where V is the volume of distribution. CL_{CR} was corrected for body surface area. Blood and urine creatinine concentrations were assayed by the method of Jaffe; meropenem did not interfere with the creatinine assay.

No medication was allowed for subjects with healthy renal functions. Patients taking barbiturates, phenytoin, rifampin, antacids, and calcium salts were excluded from the study. Patients requiring antihypertensive medication and/or diuretics were accepted providing these therapies had not been modified in the previous 3 months. Beverages containing alcohol or caffeine were not permitted during the study. Smoking was not allowed for 1 h before and 3 h after drug infusion.

Study design. All subjects fasted overnight before the study and for 3 h after meropenem administration. Each was given a single i.v. dose of 500 mg of meropenem as a 30-min infusion. Three hours after dosing, all subjects had breakfast; thereafter, food and drink were available ad libitum.

Sampling. Blood samples were collected into Vacutainer tubes containing lithium heparin as an anticoagulant.

From healthy subjects, blood samples were drawn at 0, 10, and 30 min and at 1, 2, 3, 4, 6, 9, 12, and 24 h after the

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TABLE 1. Data on volunteers and patients[a]

Group	Renal function	Age (yr)	Wt (kg)	CL_{CR} (ml/min/1.73 m^2)
Control ($n = 6$)	Healthy	33.8 ± 9.0	66.9 ± 12.4	122.5 ± 13.6
1 ($n = 6$)	Moderate impairment	49.0 ± 15.5	63.6 ± 7.6	17.1 ± 4.3
2 ($n = 4$)	Severe impairment	54.8 ± 13.6	65.5 ± 10.8	6.1 ± 1.7
3 ($n = 6$)	Hemodialysis	59.2 ± 5.1	58.7 ± 8.0	—[b]

[a] Values are means ± standard deviations.
[b] —, anuric patients.

dose. Urine samples were collected during four periods: from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after drug administration.

From uremic patients, blood samples were collected at the same times as from the control group, but further samples were drawn at 36 and 48 h in the three groups of patients. Five urine collections were obtained during 48 h (groups 1 and 2).

In hemodialysis patients (group 3), the kinetic study was performed with patients both off and on hemodialysis after a single i.v. dose of 500 mg of meropenem. These patients were studied 1 day immediately after a maintenance hemodialysis and 8 days later during a routine hemodialysis session. The session started 2 h after dosing. Samples from both the arterial and the venous lines of the dialyzer were taken at 30 min and at 1, 2, 3, and 4 h after the beginning of the session to calculate the extraction coefficient and the dialysis clearance (CL_D) of the drug. The mean hematocrit of the patients was 0.27 ± 0.05. Hemodialysis was performed with a cuprophane membrane, the ultrafiltration rate was 650 ± 195 ml/h, the blood flow rate averaged 233 ± 26 ml/min, and the mean dialysate flow rate was 533 ± 52 ml/min.

Plasma and urine samples were stored frozen at −80°C until assay.

Assay technique. The concentrations of unchanged meropenem (ICI 194,660) in plasma and urine were measured by two assay methods: a microbiological method (MBA) and a high-performance liquid chromatography method (HPLC).

The MBA was performed by using *Escherichia coli* NIHJ as the test strain. The medium used was nutrient agar (Difco Laboratories; pH 6.6). Standards were prepared with pooled human serum for plasma samples and with phosphate buffer (pH 7) for urine samples. No significant difference was observed in the antimicrobial activities of meropenem measured in plasma or serum samples, so a pooled human serum sample without antibiotic could be used as the diluent of the plasma samples. The plates were incubated overnight at 37°C. Linear regression analysis of the standard calibration lines obtained by plotting log antibiotic concentrations versus zone diameters of inhibition indicated excellent linearity of the assay between 0.08 and 5.00 μg/ml. The sensitivity limit of the assay was 0.08 μg/ml. The coefficients of variation of the assay were 5% at 5 μg/ml and 9% at 0.08 μg/ml.

The HPLC method was performed by ICI Pharmaceuticals, Macclesfield, United Kingdom (1). It was based on solid-phase extraction (for plasma samples) and reverse-phase chromatography with detection by UV A_{296}. The limit of detection of the assay procedure was 0.06 μg/ml for plasma assays and 10 μg/ml for urine assays, with an interassay coefficient of variation of less than 6%.

ICI 213,689 concentrations in plasma were measured by radioimmunoassay (RIA) using a high-specific-activity ^{125}I-radiotracer and an antiserum raised in sheep. The assay

involves mixing sample or standard (10:1) with antiserum (100:1) and radiotracer solution (100:1), both in phosphate buffer (pH 7.4, 0.1 M, containing bovine gamma globulins [0.2%]). The solution is then mixed and incubated at room temperature for 45 min. Bound and free radioactivities were separated by the addition of a polyethylene glycol 6000 solution (0.5 ml, 27.5% [wt/vol]), vortex mixing, and centrifugation at 2,800 × g for 15 min at room temperature. The supernatant was aspirated to waste, and radioactivity in the protein precipitate was counted in a gamma counter. ICI 213,689 concentrations in samples were determined by interpolation with a calibration graph constructed by plotting percent radiotracer bound against log concentration. The assay is specific for the metabolite (less than 2% cross-reactivity with meropenem) and has a limit of detection of 0.025 μg/ml. The interassay coefficient of variation was 15% across the working range of approximately 0.075 to 3 μg/ml.

Pharmacokinetic analysis. HPLC data on plasma meropenem concentration versus time were analyzed by noncompartmental methods (5). The peak concentrations in plasma (C_{max}) were the experimental values. The best log-linear fit to the terminal portion of the plasma concentration-time curve was determined by least-squares linear regression analysis to determine the elimination rate constant (β). The terminal half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/\beta$. The area under the plasma curve (AUC) was determined by the trapezoidal rule and was extrapolated to infinity. Total body clearance (CL) was calculated as $CL = dose/AUC_{0-\infty}$. The mean residence time (MRT) in the body was calculated from the formula of Yamaoka et al. (12): $MRT = \int t \, Cdt/AUC_{0-\infty}$, where $\int t \, Cdt$ is the area under the first-moment curve and $AUC_{0-\infty}$ is the AUC extrapolated to infinity. The MRT equivalent for bolus i.v. administration was calculated as MRT (i.v.) = $MRT - t/2$, in which t is the infusion time, i.e., 0.50 h (12). The volume of distribution at steady state (V_{ss})
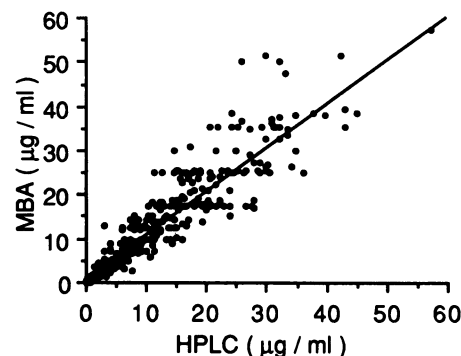

FIG. 1. Regression line between results of HPLC and MBA with unchanged meropenem. MBA = 1.03 HPLC + 1.11 ($n = 354$; $r = 0.92$).

TABLE 2. Meropenem (ICI 194,660) pharmacokinetic data for subjects with healthy and impaired renal functions after single i.v. dose of 500 mg[a]

Subjects	C_{max} (μg/ml)	AUC (μg · h/ml)	V_{SS} (liter/kg)	$t_{1/2}$ (h)	MRT (h)	CL (ml/min/1.73 m²)	CL_R (ml/min/1.73 m²)	X_u 24 h[b] (%)
Healthy	21.1 ± 10.7	28 ± 15	0.39 ± 0.10	1.24 ± 0.18	1.44 ± 0.23	328 ± 95	252 ± 74	69.3 ± 10.4
Group 1	25.4 ± 10.8	143 ± 66	0.42 ± 0.24	4.59 ± 1.23	6.28 ± 1.13	77 ± 48	29 ± 19	27.1 ± 4.0
Group 2	27.2 ± 2.9	203 ± 45	0.30 ± 0.07	5.73 ± 0.94	8.08 ± 1.68	42 ± 8	12 ± 5	22.9 ± 2.4
Group 3[c]	42.5 ± 8.5	416 ± 67	0.28 ± 0.13	10.03 ± 4.18	13.72 ± 6.17	22 ± 3		
P	0.01	<0.001	0.25	<0.001	<0.001	<0.001	0.002	0.002

[a] Values are means ± standard deviations and were determined by HPLC.
[b] X_u 24 h, renal excretion of unchanged meropenem over 24 h.
[c] Anuric patients.

was obtained as V_{SS} = MRT (i.v.) · CL. CL_R meropenem was calculated by the ratio of the unchanged amount of drug excreted in urine to the plasma AUC during the same time intervals. CL_D was calculated by the method of Gotch (6): CL_D = [Qp · C_A − (Qp − Quf) · C_V]/C_A, where C_A and C_V are concentrations of meropenem in plasma in arterial and venous lines, respectively; Qp is the plasma flow calculated by the relation Qp = Qb (1 − Hte), Qb is the blood flow, and Hte is the hematocrit; and Quf is the ultrafiltration rate.

The extraction ratio by hemodialysis (ERD) was calculated by the relation ERD = CL_D/[Qp + (Qp − Quf)]/2.

Statistical analysis. The nonparametric Kruskal-Wallis test was used to analyze differences between the group means. P values lower than 0.05 were considered statistically significant.

RESULTS

Concentrations of the unchanged drug in HPLC and MBA were linearly correlated. The equation of the regression line obtained was MBA = 1.03 HPLC + 1.11 (n = 354; r = 0.92) (Fig. 1). The pharmacokinetic parameters of unchanged meropenem were calculated by using the HPLC data.

Healthy subjects. The pharmacokinetic data of unchanged meropenem for the six subjects with healthy renal functions receiving a single i.v. dose of 500 mg while they were fasting are shown in Table 2. The peak levels in plasma were 21.1 ± 10.7 μg/ml, and the AUC averaged 28 ± 15 μg · h/ml. The V_{SS} was 0.39 ± 0.10 liter/kg. The $t_{1/2}$ was 1.24 ± 0.18 h. CL and CL_R were 328 ± 95 and 252 ± 74 ml/min, respectively. Renal excretion of unchanged meropenem accounted for 69.3 ± 10.4% of the dose in 24-h urine samples.

The concentrations of the metabolite in plasma as measured by RIA were low in healthy subjects (C_{max} = 1.6 ± 0.6 μg/ml) and the apparent $t_{1/2}$ was 2.8 ± 0.9 h (Table 3).

Uremic patients. The mean C_{max} significantly increased only in group 3 patients (42.5 ± 8.5 versus 21.1 ± 10.7 μg/ml in the control group) (P = 0.01).

The $t_{1/2}$ increased with increasing renal impairment, reach-

ing values 10-fold higher than those obtained in healthy subjects (10 h in group 3 versus 1.2 h in healthy subjects; P < 0.001) (Fig. 2).

In a previous paper concerning the pharmacokinetic study of meropenem in 10 patients with CL_{CR} of 33 to 74 ml/min, the mean $t_{1/2}$ calculated from MBA data was twofold higher than that obtained in subjects with healthy renal function (1.93 ± 0.81 h) (8).

In the present study, an increase in MRT corresponded to a decrease in renal function. The V_{SS} was not statistically influenced by renal impairment. The pharmacokinetic data of unchanged meropenem are summarized in Table 2. The concentrations of the metabolite (ICI 213,689) in plasma significantly increased in relation to the degree of renal dysfunction; C_{max} values were 6.7 ± 4.6 and 10.8 ± 1.4 μg/ml in groups 1 and 3, respectively. The apparent $t_{1/2}$ increased from about 3 h in healthy subjects to about 35 h in group 2 patients (Table 3, Fig. 3).

Hemodialysis patients. The pharmacokinetic data of meropenem were calculated in both the predialysis and the dialysis periods for hemodialysis patients (Tables 3 and 4). During a 4-h hemodialysis session, the determination of levels in plasma in both the venous and the arterial lines permitted us to calculate the dialysances of meropenem and its metabolite; they were 81 ± 22 ml/min (HPLC data; n = 6) and 89 ± 10 ml/min (RIA data; n = 6), respectively. The ERD of unchanged meropenem was 0.51 ± 0.20. Meropenem and its metabolite were readily removed by hemodialysis. It is to be noted that the metabolite was removed over four successive dialysis sessions after the single dose of meropenem.

TABLE 3. Metabolite (ICI 213,689) pharmacokinetic data for subjects with healthy and impaired renal functions after single i.v. dose of 500 mg[a]

Subjects	C_{max} (μg/ml)	AUC (μg · h/ml)	$t_{1/2}$ (h)
Healthy	1.6 ± 0.6	4.5 ± 1.4	2.8 ± 0.9
Group 1	6.7 ± 4.6	127 ± 26	24.0 ± 15.9
Group 2	4.8 ± 1.5	178 ± 71	34.9 ± 19.3
Group 3	10.8 ± 1.4	391 ± 100	>40

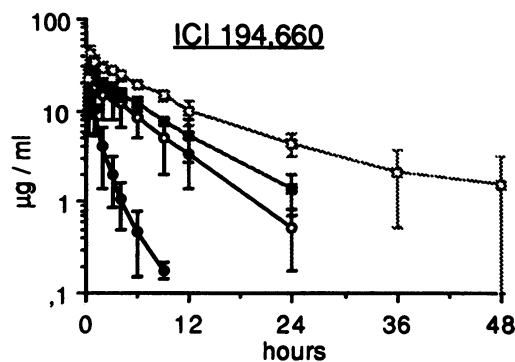[a] Values are means ± standard deviations and were determined by RIA.

FIG. 2. Curves for meropenem (ICI 194,660) level in plasma versus time in subjects with healthy renal functions and in three groups of uremic patients (values are means ± standard deviations). ●, control group; ○, group 1; ■, group 2; □, group 3.
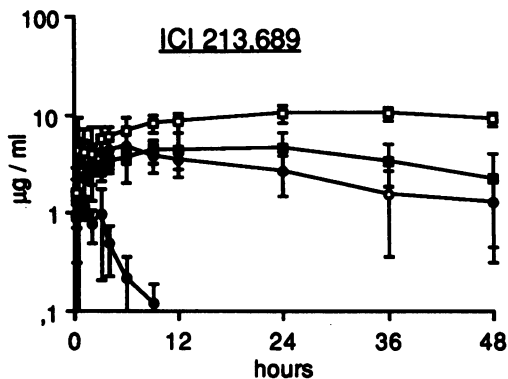
FIG. 3. Curves for metabolite (ICI 213,689) level in plasma versus time in subjects with healthy renal functions and in three groups of uremic patients (values are means ± standard deviations). ●, control group; ○, group 1; ■, group 2; □, group 3.

FIG. 4. Regression line between CL and CL_{CR} of meropenem after a single i.v. dose of 500 mg.

DISCUSSION

Healthy subjects. In healthy subjects, the pharmacokinetic parameters of meropenem found in our study were in good agreement with those reported by other authors (1, 2). Meropenem is mainly excreted in urine in an unchanged form, indicating the drug's excellent stability against renal dehydropeptidase I. CL_R exceeded CL_{CR} (CL_R/CL_{CR} = 2.03 ± 0.46), suggesting that renal excretion is by both glomerular filtration and tubular secretion.

Uremic patients. Results obtained in our study for uremic patients correlate well with those recently published by others (3).

The peak levels of unchanged meropenem in plasma were higher in group 3 patients than in the three other groups of subjects (P = 0.01); this increase is related to the lack of renal elimination in this group and cannot be explained by differences in body weights, which were not statistically different (P = 0.58). The meropenem $t_{1/2}$ and MRT increased in relation to the degree of renal impairment, reaching values 10-fold higher than those found in subjects with healthy renal function (10 h in group 3 versus 1.2 h in healthy subjects). The V_{SS} of the unchanged drug is not significantly modified in uremic patients (P = 0.25). CL from plasma and CL_R of meropenem decreased in uremic patients and are linearly related to CL_{CR} (Fig. 4 and 5). The nonrenal elimination of meropenem increased in patients with renal impairment from 22% ± 12% CL in the control group to 62% ± 3% and 72% ± 8% in groups 1 and 2, respectively, as indicated by the important increase in the concentrations in plasma and in the $t_{1/2}$ of the metabolite in patients with end-stage renal failure (Table 3).

Recommendations regarding dosages of meropenem according to the degree of renal impairment may be proposed on the basis of excellent linearity of the relation between CL and CL_R of meropenem and CL_{CR} (Fig. 4 and 5) and of
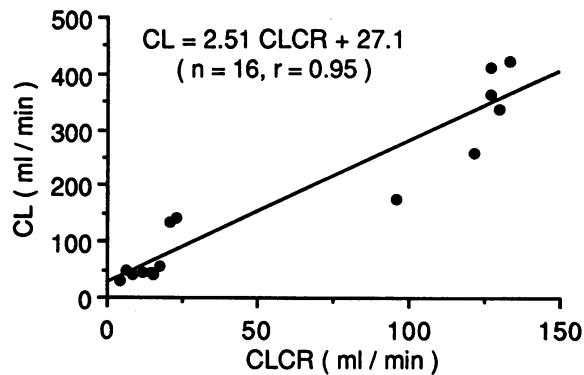
simulated multiple-dose kinetics. In order to achieve mean steady-state concentrations in plasma of about 4 μg/ml (i.e., four times higher than the mean MIC for the most susceptible bacteria), the following dosage recommendations could be proposed in the treatment of systemic infections: for a CL_{CR} of >80, 1.0 dose every 6 to 8 h; for a CL_{CR} of 30 to 80, 1.0 dose every 8 to 12 h; and for a CL_{CR} of 10 to 30, 0.5 to 1.0 dose every 12 h. For a CL_{CR} of <10, 1.0 dose every 24 h would suffice.

An additional dose at the end of each hemodialysis session is needed, since meropenem and its metabolite are readily cleared by hemodialysis.

Further clinical multiple-dose studies are necessary to confirm these dosage recommendations and to control the lack of accumulation of unchanged meropenem and of its metabolite during treatment.

In conclusion, the pharmacokinetic study of meropenem and its metabolite in subjects with healthy and impaired renal functions has shown that the elimination parameters are affected by the degree of renal failure. An important accumulation of the metabolite was observed in the plasma of uremic patients. A good correlation was found between the two assay techniques used for determining concentrations of the active drug in plasma. In the treatment of systemic infections, dosage adjustments of meropenem will be necessary according to the degree of renal impairment.
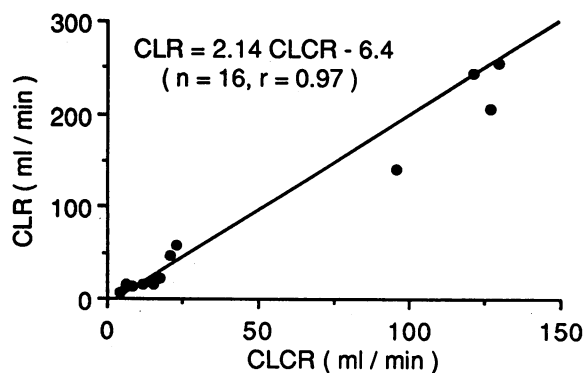
TABLE 4. Meropenem pharmacokinetic data during hemodialysis[a]

Substance	Assay	C_{max} (μg/ml)	CL_D (ml/min)	ERD
ICI 194,660	HPLC	26.0 ± 9.2	81 ± 22	0.51 ± 0.20
ICI 213,689	RIA	5.0 ± 4.3	88 ± 10	0.56 ± 0.13

[a] Values are means ± standard deviations.

FIG. 5. Regression line between CL_R and CL_{CR} of meropenem after a single i.v. dose of 500 mg.

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