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Disposition of Radiolabeled Imipenem and Cilastatin in Normal Human Volunteers

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In the first of two successive studies, four healthy male subjects received 500 mg of ^{14}C-labeled imipenem alone and together with 500 mg of unlabeled cilastatin sodium. In the second study, the same subjects were given 250 mg of ^{14}C-labeled cilastatin sodium alone and together with 250 and 1,000 mg of cold imipenem. Concentrations of imipenem and cilastatin in plasma, urine, and feces were assayed by high-pressure liquid chromatography and radiometry. Plasma concentrations of imipenem assayed radiometrically were higher than those measured by high-pressure liquid chromatography. In one subject studied at the end of drug administration, the open lactam metabolite of imipenem represented 9% of the radioactivity. Plasma levels of cilastatin determined by high-pressure liquid chromatography and radiometry were virtually identical. Urinary recovery of imipenem varied between 12 and 42% of the dose when that drug was given alone but increased to between 64 and 75% when administered with cilastatin sodium at a 1:1 ratio. Almost all radioactivity of imipenem was recovered in the urine within 96 h after drug administration. The open lactam metabolite, resulting from the metabolism of imipenem in the kidneys by a dipeptidase, dehydropeptidase-I, represented 80 to 90% of the effluent radioactivity when imipenem was given alone and about 20% when cilastatin sodium was coadministered. Renal excretion of cilastatin followed closely that of imipenem. Almost all of the administered radioactivity was recovered in 24 h, and about 75% of the dose was recovered as unchanged cilastatin within 6 h. The *N*-acetyl metabolite of cilastatin was found to represent about 12% of the total radioactivity.

Imipenem is a carbapenem antibiotic with a broad antibacterial spectrum, including enterococci, *Pseudomonas aeruginosa*, and *Bacteroides fragilis* (4, 7). In animals, imipenem has been found to be excreted renally but also to be metabolized in the kidneys by a dipeptidase, dehydropeptidase I (DHP-I), located on the brush border of the proximal tubular cells (4). Similar metabolism occurs in humans, resulting in variable urinary recovery (5 to 40% of the administered imipenem doses) with a marked intersubject but a minimal intrasubject variability (6). This metabolism is inhibited by cilastatin, an inhibitor of DHP-I (3). In humans, coadministration of imipenem with cilastatin sodium results in an increase of the urinary recovery of imipenem to about 70% of the dose, irrespective of the degree of metabolism when imipenem is given alone (5). It has been suggested that the imipenem which cannot be recovered in the urine undergoes systemic metabolism (5, 6). The present investigation was undertaken to elucidate the metabolic disposition and excretion of imipenem and cilastatin by using radiolabeled imipenem or cilastatin sodium.

MATERIALS AND METHODS

Both studies described here were approved by the Ethical Review Committee and the Isotope Committee of the Faculty of Medicine, University of Umeå, Umeå, Sweden, and all volunteers gave written, informed consent to their participation in the study.

Subjects. Four healthy male volunteers (ages, 30 to 31 years; body weights, 71 to 87 kg [mean, 78 kg]; heights, 180 to 192 cm [mean, 183 cm]) who had previously participated in studies with imipenem and cilastatin (5) were selected. In two of the subjects, urinary recovery of imipenem administered alone was <16% of the dose, and in two subjects, urinary recovery was >16% of the dose. These pairs of individuals have been referred to subsequently as high and low metabolizers.

Treatments. All subjects received five treatments (A through E) with intervals of 2 weeks between treatments A and B, C and D, and D and E and 1 year between treatments B and C. Treatment A consisted of 500 mg of ^{14}C-labeled

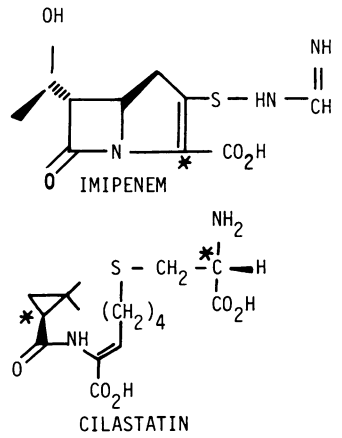

FIG. 1. Structure of imipenem and cilastatin. Asterisks mark the location of the ^{14}C label.

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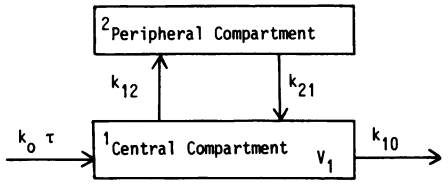

FIG. 2. Two-compartment open model used for the calculation of kinetic parameters. For explanation of symbols, see text.

imipenem (20 μCi) alone. Treatment B consisted of 500 mg of ^{14}C-labeled (20 μCi) imipenem plus 500 mg of cilastatin sodium. Treatment C consisted of 250 mg of ^{14}C-labeled cilastatin sodium (20 μCi) alone. Treatment D consisted of 250 mg of imipenem plus 250 mg of ^{14}C-labeled cilastatin sodium (20 μCi). Treatment E consisted of 1,000 mg of imipenem plus 250 mg of ^{14}C-labeled cilastatin sodium (20 μCi).

Unlabeled and radiolabeled imipenem and cilastatin sodium were provided by Merck, Sharp & Dohme Research Laboratories, West Point, Pa. The locations of the radiolabels are given in Fig. 1. All doses were administered as intravenous infusions over 20 min with a constant-infusion syringe pump and a total volume of 100 ml. Imipenem was dissolved in saline or in a solution of cilastatin sodium in saline. The same solution of cilastatin sodium in saline was also used when cilastatin was given alone.

All subjects had been fasting for at least 10 h before the administration of each dose but were allowed water ad libitum. They received a standard snack and a standard lunch 2 and 4 hours, respectively, after the infusions. A physical examination was performed before and after each dose was administered. Laboratory safety profiles were obtained before and after each dose. The glomerular filtration rate (GFR) was determined in each subject during each treatment by the [^{51}Cr]EDTA technique. Blood samples for analysis of imipenem or cilastatin or both were collected before and at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 10, 24, 48, 72, and 96 h after the beginning of each infusion. Urine was collected

TABLE 1. Individual and mean plasma concentrations of imipenem after administration of imipenem alone (treatment A) or as a 1:1 combination with cilastatin (treatment B)

Subject no.	Time (h)	Imipenem concn[a] determined by:			
		HPLC		Radiometry	
		Treatment A	Treatment B	Treatment A	Treatment B
1	0.33	25.8	44.0	32.2	34.2
	0.67	15.4	24.5	22.0	21.2
	1.0	15.1	21.7	17.4	17.4
	2.0	5.8	13.5	10.0	11.0
	4.0	1.9	1.9	4.4	4.3
	6.0	ND[b]	ND	2.4	2.3
	10.0	ND	ND	1.2	1.2
2	0.33	44.3	29.4	37.8	29.3
	0.67	21.7	28.9	23.5	24.4
	1.0	15.1	15.7	17.8	18.5
	2.0	6.3	3.9	10.8	11.0
	4.0	2.2	1.5	4.9	4.7
	6.0	ND	ND	2.4	2.3
	10.0	ND	ND	1.2	1.4
3	0.33	32.6	34.5	37.8	36.5
	0.67	17.6	17.4	23.1	22.6
	1.0	10.1	11.4	17.0	17.1
	2.0	2.7	4.3	9.0	9.1
	4.0	ND	ND	4.2	4.2
	6.0	ND	ND	2.3	2.4
	10.0	ND	ND	1.2	1.1
4	0.33	28.3	32.3	31.2	34.9
	0.67	19.2	18.3	21.9	20.9
	1.0	11.9	12.4	16.6	16.1
	2.0	2.4	5.3	9.1	9.8
	4.0	ND	1.2	3.8	4.4
	6.0	ND	ND	2.1	2.3
	10.0	ND	ND	1.0	1.0
1 to 4	0.33	32.8 ± 8.2[c]	35.1 ± 6.3	34.8 ± 3.5	33.7 ± 3.1
	0.67	18.5 ± 2.7	22.3 ± 5.4	22.6 ± 0.8	22.3 ± 1.6
	1.0	13.1 ± 2.5	15.3 ± 4.7	17.2 ± 0.5	17.7 ± 0.7
	2.0	4.3 ± 2.0	6.8 ± 4.5	9.7 ± 0.8	10.2 ± 0.9
	4.0	ND	ND	4.3 ± 0.5	4.7 ± 0.5
	6.0	ND	ND	2.3 ± 0.1	2.5 ± 0.3
	10.0	ND	ND	1.2 ± 0.1	1.0 ± 0.4

[a] Concentration in micrograms per milliliter or micrograms equivalent per milliliter.
[b] ND, Not detectable.
[c] Mean ± SD.

TABLE 2. Individual and mean plasma concentrations of cilastatin after administration of cilastatin alone (treatment C) or together with imipenem at an imipenem-cilastatin ratio of 1:1 (treatment D) or 4:1 (treatment E)

Subject no.	Time (h)	Cilastatin concn[a] as determined by:					
		HPLC			Radiometry		
		Treatment C	Treatment D	Treatment E	Treatment C	Treatment D	Treatment E
1	0.33	23.0	20.5	23.4	21.7	20.8	22.8
	0.67	12.5	13.3	12.8	12.7	13.3	11.9
	1.0	7.7	8.7	9.5	8.2	8.7	9.1
	2.0	2.7	3.5	3.3	3.4	4.2	3.9
	4.0	ND[b]	ND	ND	0.9	1.0	0.9
	6.0	ND	ND	ND	0.3	0.4	0.3
	10.0	ND	ND	ND	0.05	0.09	ND
2	0.33	23.8	21.9	21.4	24.0	17.9	21.0
	0.67	13.8	13.4	14.0	14.7	12.8	13.5
	1.0	10.2	9.5	9.2	9.9	9.3	9.9
	2.0	3.7	3.6	3.9	4.3	4.0	4.2
	4.0	1.0	0.8	1.2	1.2	1.1	1.5
	6.0	ND	ND	ND	0.3	0.3	0.4
	10.0	ND	ND	ND	0.04	ND	0.05
3	0.33	21.4	25.7	25.3	20.6	21.6	21.4
	0.67	11.7	12.4	13.2	11.0	11.2	11.2
	1.0	5.9	7.9	8.2	6.1	7.5	7.4
	2.0	2.0	2.6	2.4	2.6	2.8	2.4
	4.0	ND	ND	ND	0.6	0.7	0.6
	6.0	ND	ND	ND	0.2	0.2	0.2
	10.0	ND	ND	ND	ND	0.08	0.07
4	0.33	21.2	21.6	19.2	20.1	20.4	18.7
	0.67	11.1	10.3	10.2	10.3	9.9	10.0
	1.0	7.7	6.5	6.8	7.0	6.4	7.4
	2.0	3.4	2.7	3.3	3.4	2.9	4.0
	4.0	0.9	ND	ND	0.9	0.8	1.1
	6.0	ND	ND	ND	0.3	0.2	0.3
	10.0	ND	ND	ND	0.06	0.08	0.1
1 to 4	0.33	22.4 ± 1.3[c]	22.4 ± 2.3	22.3 ± 2.6	21.6 ± 1.7	20.2 ± 1.6	21.0 ± 1.7
	0.67	12.3 ± 1.2	12.3 ± 1.4	12.5 ± 1.7	12.2 ± 2.0	11.8 ± 1.6	11.7 ± 1.5
	1.0	7.9 ± 1.8	8.1 ± 1.3	8.3 ± 1.2	7.8 ± 1.6	8.0 ± 1.3	8.5 ± 1.3
	2.0	2.9 ± 0.8	3.1 ± 0.5	3.3 ± 0.6	3.4 ± 0.7	3.5 ± 0.7	3.6 ± 0.8
	4.0	ND	ND	ND	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.4
	6.0	ND	ND	ND	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
	10.0	ND	ND	ND	ND	ND	ND

[a] Microgram equivalents per milliliter.
[b] ND, Not detectable.
[c] Mean ± SD.

before and at 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 24, 24 to 36, 36 to 48, 48 to 72, 72 to 96, and 96 to 120 h after the start of each infusion. Feces was collected at 120 h after each infusion. Blood samples obtained through 10 h were stabilized in morpholineethanesulfonate buffer and ethylene glycol as previously described (6) and were frozen at −80°C for subsequent radiometric and high-pressure liquid chromatographic (HPLC) analyses of imipenem. In treatments B, C, D, and E, a portion of each plasma sample was stored unstabilized at −20 or −80°C for analysis of cilastatin by radiometric or HPLC analyses. The remaining plasma samples, obtained through 96 h, were stored unstabilized at −20°C for radiometric assays of imipenem or cilastatin. Urine samples obtained during the initial 10 h after each treatment were quantified, a sample was drawn and mixed with an equal volume of a 1:1 mixture of morpholinopropane sulfonate buffer (pH 6.8)-ethylene glycol before freezing at −80°C. The remaining urine samples were frozen unstabilized at −20°C for radiometric analysis.

Radiometric methodology. The radioactivities of infusion solutions and plasma and urine samples were measured by direct liquid scintillation counting in a Packard Tricarb scintillation spectrometer operated at settings optimal for ^{14}C activity. Fecal specimens, homogenized in a known volume of water, were assayed radiometrically after alkaline digestion and hydrogen peroxide decolorization. The scintillation solution was Amersham PCS (Amersham, Oakville, Ontario, Canada). All samples were counted for a minimum of 5 min or 900,000 counts. Background ranged from 35 to 43 cpm for the various control specimens. The minimum level of radioactivity used in calculations was 7 cpm above that of the background. Quenching corrections were made on all samples by the external standard technique and were verified by random internal standardization with [^{14}C]toluene. The percent efficiency of counting ranged from 63 to 88% for all samples.

HPLC determination of imipenem. Imipenem concentrations were determined by a reverse-phase HPLC methodology for plasma samples and cation-exchange HPLC methodology for urine samples (D. A. Gravallese, D. G. Musson,

TABLE 3. Individual pharmacokinetic parameters for imipenem and cilastatin[a]

Subject no.	Dose of (mg)		Parameter[b]													
			α (h^{-1})		β (h^{-1})		k_{21} (h^{-1})		k_{12} (h^{-1})		k_{10} (h^{-1})		AUC (μg h/ml)		V_1 (liters)[b]	
	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
1	500	0	7.5	NA[c]	0.7	NA	4.2	NA	2.8	NA	1.2	NA	32.7	NA	12.4	NA
	500	500	4.8	2.9	0.6	0.7	2.4	1.7	1.8	0.7	1.2	1.2	51.7	39.8	7.8	10.3
	0	250	NA	4.4	NA	0.9	NA	2.6	NA	1.2	NA	1.5	NA	21.0	NA	7.8
	250	250	7.2	3.5	0.8	0.9	5.9	2.8	1.2	0.5	1.0	1.2	24.2	22.3	10.3	9.6
	1,000	250	4.2	7.8	0.6	0.9	2.6	4.2	1.3	2.9	0.9	1.6	88.0	24.8	12.4	6.4
2	500	0	4.7	NA	0.6	NA	1.9	NA	1.9	NA	1.5	NA	46.2	NA	7.2	NA
	500	500	1.8	3.8	0.7	0.7	1.5	2.3	0.2	1.0	0.9	1.2	40.3	48.8	14.1	8.5
	0	250	NA	2.4	NA	0.7	NA	1.6	NA	0.5	NA	1.1	NA	25.4	NA	9.1
	250	250	2.7	2.9	0.8	0.8	1.9	2.0	0.5	0.5	1.1	1.1	19.9	24.2	11.1	9.1
	1,000	250	[d]	2.9	[d]	0.7	[d]	1.7	[d]	0.7	[d]	1.1	[d]	26.1	[d]	8.6
3	500	0	2.7	NA	1.0	NA	1.5	NA	0.5	NA	1.7	NA	26.2	NA	11.4	NA
	500	500	4.5	3.1	0.9	0.8	2.6	1.7	1.3	0.8	1.6	1.5	30.3	34.5	10.2	9.8
	0	250	NA	3.5	NA	0.8	NA	1.5	NA	0.9	NA	1.9	NA	17.8	NA	7.4
	250	250	[e]	3.0	1.0	0.8	[e]	1.4	[e]	0.7	[e]	1.6	23.1	22.2	11.2	7.2
	1,000	250	2.7	3.4	0.5	0.8	1.0	1.6	0.9	1.0	1.4	1.6	59.0	23.8	12.5	6.8
4	500	0	2.3	NA	0.8	NA	1.9	NA	0.3	NA	1.0	NA	32.8	NA	14.9	NA
	500	500	3.9	4.1	0.8	0.8	2.3	2.3	1.1	1.2	1.3	1.4	33.2	36.7	11.4	9.7
	0	250	NA	3.2	NA	0.7	NA	1.7	NA	0.9	NA	1.3	NA	20.8	NA	9.4
	250	250	1.9	5.4	0.7	0.8	1.5	2.5	0.2	1.9	0.9	1.8	21.6	19.5	12.6	7.1
	1,000	250	5.6	5.6	0.6	0.8	2.8	2.9	2.2	2.0	1.3	1.5	86.0	20.2	9.1	8.2

[a] Plasma concentrations of imipenem (I) and cilastatin (C) were determined by HPLC analysis.
[b] α, Distribution phase; β, elimination phase; other parameters are as defined in the text.
[c] NA, Not applicable.
[d] Nonconstant clearance.
[e] Monoexponential fit.

L. T. Pauliukonis, and W. F. Bayne, J. Chromatogr, in press). Stabilized samples were stored at −70°C until the time of analysis. Plasma and urine samples were prepared for injection by ultrafiltration through an Amicon CF50A membrane cone. For plasma, the standard concentration curve ranged from 1.0 to 100 μg/ml, and for urine, it ranged from 2.0 to 200 μg/ml. The sensitivity of the plasma assay was 1.0 μg/ml, and for urine the lower limit was 2.0 μg/ml. Both assay methods separate thienamycin from imipenem, which is the *N*-formimidoyl derivative of thienamycin.

HPLC determination of cilastatin. Concentrations of cilastatin in plasma and urine specimens were determined by HPLC analysis. The procedure combined reverse-phase chromatography with postcolumn derivatization of cilastatin and the internal standard with orthophthalaldehyde-mercaptoethanol and the fluorescence detection of the resulting isoindole fluorophores (J. L. Demetriades et al., manuscript in preparation). The method was specific for cilastatin without interference from the *N*-acetyl metabolite based on the selective derivatization of primary amines.

Nonstabilized samples (treatments B and C) were stored at −20°C until time of analysis, whereas stabilized samples (treatments D and E) were stored at −70°C. Since cilastatin in combination with imipenem is stable in plasma when stored at −20°C, these specimens did not require stabilization. However, the addition of stabilizer to plasma did not interfere with the analytical procedure. Urine samples, containing both imipenem and cilastatin, must be stabilized since imipenem or its degradates or both adversely affect the in vitro stability of cilastatin.

Standard curves of cilastatin in the appropriate control fluid were linear from 0.75 to 75.00 μg/ml in plasma and from 2.5 to 200.0 μg/ml in urine. The mean intraday coefficients of variation (n = 6 determinations at each concentration of the daily standard curve) were 4.6% for plasma analyses and 4.2% for urine analyses. The limits of reliable detection were 0.75 μg/ml in plasma and 2.5 μg/ml in urine. Calculated concentrations less than these values were reported to be zero.

HPLC determination of *N*-acetyl cilastatin. *N*-Acetyl and *N*-propyl (internal standard) cilastatin from urine were absorbed on an anion-exchange extraction column and then eluted with 1 M sodium chloride solution. The analyses were performed on an HPLC system with a Spectroflow 757 UV detector operated at 210 nm. The analytical column (25 cm by 4.6 mm i.d.) was packed with 5 μm Ultrasphere octadecylsilane. The mobile phase was a mixture of methanol–acetonitrile to 0.85% phosphoric acid buffer (8:2:15, by volume) adjusted to pH 4.0 with triethylamine. The flow rate was 1.0 ml/min. The presence of imipenem and cilastatin did not interfere with the quantitative determination of *N*-acetyl cilastatin. Calibration curves constructed by plotting peak height ratios relative to the internal standard showed a linear relationship at concentrations ranging from 10 to 500 μg/ml. Over this concentration range, *N*-acetyl cilastatin could be measured with interday coefficients of variation ranging from 1 to 7%.

Pharmacokinetic analyses. The area under the plasma concentration-time curve (AUC) for individual imipenem and cilastatin plasma data obtained after each treatment was estimated from best-fit pharmacokinetic parameters. Individual pharmacokinetic parameters for imipenem and cilastatin in each treatment were derived by a general curve-stripping technique to compute the least-squares fit for an exponential function. The disposition of both imipenem and cilastatin is adequately described by a two-compartment

TABLE 4. Individual and mean urinary recovery of imipenem after administration of imipenem alone (treatment A) or together with cilastatin (treatment B)

Subject no.	Collection period (h)	Imipenem urinary recovery[a] as determined by:			
		HPLC		Radiometry	
		Treatment A	Treatment B	Treatment A	Treatment B
1	0–2	9.6	54.3	63.2	59.6
	2–4	2.1	12.8	20.4	21.0
	4–6	0.5	2.7	7.5	8.6
	6–10	0.1	0.9	5.1	5.9
	10-24	ND[b]	ND	2.7	6.3
	24–48	ND	ND	1.5	1.5
	0–48	12.3	70.7	100.4	102.9
2	0–2	10.9	56.6	64.3	63.5
	2–4	2.1	11.4	19.3	20.6
	4–6	0.6	2.1	8.0	7.8
	6–10	0.2	0.7	5.1	4.7
	10-24	ND	ND	4.5	3.1
	24–48	ND	ND	1.6	1.9
	0–48	13.8	70.8	102.8	101.6
3	0–2	16.8	52.6	66.3	64.2
	2–4	2.3	8.3	14.9	18.6
	4–6	0.5	2.0	6.9	6.6
	6–10	0.2	1.3	4.9	8.1
	10–24	ND	ND	6.0	6.5
	24–48	ND	ND	1.1	1.3
	0–48	19.8	64.2	100.2	105.1
4	0–2	33.1	60.5	56.4	49.5
	2–4	6.1	10.7	18.4	19.0
	4–6	1.5	2.5	6.8	6.8
	6–10	1.0	1.2	4.3	4.8
	10–24	ND	ND	5.5	6.3
	24–48	ND	ND	1.0	1.3
	0–48	41.7	74.9	98.8	87.6
1 to 4	0–2	20.3±11.5[c]	56.3 ± 3.1	62.4 ± 4.3	59.2 ± 6.8
	2–4	3.2 ± 2.0	10.8 ± 1.9	18.3 ± 2.4	19.8 ± 1.2
	4–6	0.8 ± 0.5	2.3 ± 0.3	7.3 ± 0.6	7.5 ± 0.9
	6–10	0.4 ± 0.4	1.0 ± 0.3	4.9 ± 0.4	5.9 ± 1.6
	10–24	ND	ND	4.7 ± 1.5	5.6 ± 1.6
	24–48	ND	ND	1.3 ± 0.3	1.5 ± 0.3
	0–48	21.9 ± 13.6	70.2 ± 4.4	100.6 ± 1.7	99.3 ± 7.9

[a] Percentage of dose administered.
[b] ND, Not detectable.
[c] Mean ± SD.

open model, with elimination occurring from the central compartment only as shown in Fig. 2.

In this pharmacokinetic model, k_{12} and k_{21} are intercompartmental transport rate constants, k_{10} is the elimination rate constant, V_1 is the volume of the central compartment, k_0 is the infusion rate, and τ is the infusion time.

Body surface area (SA; in centimeters squared) was estimated from body weight (W; in kilograms) and height (H; in centimeters) by: $SA = W^{0.425} \times H^{0.725} \times 71.84$. The renal clearance ($VCL_R$) of imipenem and cilastatin was estimated from the corresponding increments of urinary excretion of drug and AUC, whereas the plasma clearance (VCL_p) of both drugs was calculated from pharmacokinetic parameters.

RESULTS

Safety and tolerance. All treatments were well tolerated. One subject experienced loose stools for 2 days beginning 3 days after treatment E. This event was not considered to be drug related since other members of the patient's household had similar symptoms. No other clinical or laboratory adverse events were noted.

Plasma kinetics of imipenem and cilastatin. Tables 1 and 2 show the plasma concentrations of the two drugs when assayed by HPLC, and radiometric analyses. Higher concentrations of imipenem equivalents but not of cilastatin equivalents were obtained by radiometric analysis than by HPLC analysis. Analyses of the plasma samples taken from one subject (subject 2) immediately after the end of administration of treatments A and B showed that in both samples, the open lactam metabolite of imipenem represented about 9% of the total radioactivity. Plasma levels of cilastatin or cilastatin-derived radioactivity were similar, irrespective of the dose of imipenem that was coadministered. Comparison of the high and low metabolizers (subjects 1 and 2 and subjects 3 and 4, respectively) of imipenem indicated that there were no obvious differences in the plasma kinetics of either imipenem of cilastatin.

Table 3 gives the pharmacokinetic parameters for imipenem and cilastatin. The AUC for either drug was propor-

TABLE 5. GFR, plasma and renal clearances of imipenem and cilastatin[a]

Subject no.	Dose (mg)		GFR (ml/min/1.73 m²)	UR (% dose)					VCL_P (ml/min/1.73 m²)		VCL_R (ml/min/1.73 m²)	
	I	C		I	[^{14}C]I	C	NAC	[^{14}C]C	I	C	I	C
1	500	0	104	12.3	100.4	NA[b]	NA	NA	225	NA	28	NA
	500	500	106	70.7	102.9	NC[c]	NC	NA	142	185	102	NC
	0	250	111	NA	NA	79.6	8.1	97.2	NA	175	NA	141
	250	250	111	77.6	NA	89.8	1.6	108.6	152	165	119	150
	1,000	250	110	82.0	NA	76.6	5.2	103.6	168	148	142	116
2	500	0	113	13.8	102.8	NA	NA	NA	165	NA	23	NA
	500	500	105	70.8	101.6	NC	NC	NA	189	156	137	NC
	0	250	137	NA	NA	78.1	14.2	106.6	NA	145	NA	117
	250	250	118	75.3	NA	74.0	14.4	104.9	186	153	140	114
	1,000	250	116	89.1	NA	75.0	10.5	108.3	[d]	142	[d]	109
3	500	0	136	19.8	100.2	NA	NA	NA	254	NA	50	NA
	500	500	132	64.2	105.1	NC	NC	NA	220	193	139	NC
	0	250	127	NA	NA	68.1	10.9	107.2	NA	184	NA	135
	250	250	129	89.1	NA	70.9	10.7	99.7	142	148	126	108
	1,000	250	142	76.3	NA	69.4	11.6	100.4	222	138	175	99
4	500	0	119	41.7	98.8	NA	NA	NA	222	NA	91	NA
	500	500	115	74.9	87.6	NC	NC	NA	219	198	163	NC
	0	250	126	NA	NA	74.3	13.6	99.7	NA	174	NA	133
	250	250	118	71.7	NA	77.6	15.7	99.2	168	186	120	146
	1,000	250	116	73.3	NA	83.9	15.6	102.2	168	179	126	153

[a] Plasma and renal clearances (VCL_P and VCL_R, respectively, of imipenem (I) and cilastatin (C) as calculated from HPLC determination and urinary recovery (UR; 0–48 h) of imipenem, radioactivity from [^{14}C]imipenem ([^{14}C]I), cilastatin, *N*-acetyl cilastatin (NAC), and radioactivity from [^{14}C]cilastatin ([^{14}C]C).
[b] NA, Not applicable.
[c] NC, Not calculated due to inadequate storage of samples.
[d] Nonconstant clearance.

tional to the doses administered. The AUC for imipenem increased in three of the subjects when it was given together with cilastatin sodium compared with when it was given alone. The mean plasma half-life of imipenem when administered alone was 55.5 ± 10.3 (standard deviation [SD]) min and 59.3 ± 12.4 min when it was coadministered with cilastatin. The half-life of cilastatin was similar, with a mean value of 53.7 ± 5.0 min.

Excretion of imipenem and cilastatin. Radiometric studies established that less than 2% of the radioactive dose was excreted with feces.

Table 4 shows the excretory pattern of imipenem in urine after treatments A and B. In treatment A, there were marked differences between the high and low metabolizers of imipenem, with a urinary recovery of active imipenem which varied between 12% (subject 1) and 42% (subject 4). Coadministration of cilastatin sodium with imipenem at a 1:1 ratio resulted in an increase of the urinary recovery to between 64 and 75%. The excretion of radioactivity was higher with cilastatin sodium than that with imipenem. About 93% of the radioactivity was recovered in the urine during the first 10 h after administration, and approximately another 5% was recovered during the following 14 h. At 96 h after the doses were administered about 100% of the radioactivity had been excreted renally. The excretory pattern of radioactivity was almost identical in all subjects after treatments A and B. When the urine from subject 2 was studied by chromatography of the radioactive eluate, it was found that in all the urine portions collected during treatment A, 80 to 90% of the effluent radioactivity was representative of the open lactam metabolite of imipenem. After treatment B, the radioactivity represented by that metabolite accounted for 22% of the total radioactivity in the portion obtained at 0 to 1 h and 55% in that obtained at 4 to 6 h, indicating an inhibition of the biotransformation of imipenem by cilastatin. The total urinary recovery of imipenem in treatments D and E did not decrease when the imipenem-cilastatin sodium ratio was changed from 1:1 to 4:1, with mean values of 78.4 ± 7.5 and 80.2 ± 7.0%, respectively (Table 5).

Table 5 shows that the renal clearance of imipenem was lower than the plasma clearance but higher than the GFR of the subjects. The renal clearance of imipenem after treatment A varied markedly between the subjects because of the individual variations in the degree of renal metabolism of the drug. After treatments B, D, and E, there were no obvious differences in the renal clearances of imipenem, which were consistently higher than the GFRs of the subjects.

The renal excretion of cilastatin closely followed that of imipenem, with about 76% of the dose being recovered in the urine as unchanged cilastatin 6 h after administration (Table 6). The *N*-acetyl metabolite of cilastatin was detectable in the urine during the first 3 to 4 h after administration of the doses. Almost all radioactivity was excreted during the first 10 h after dosing. The mean excretion of cilastatin plus its *N*-acetyl metabolite was 87.7 ± 5.7% of the total dose administered, whereas the mean excretion of radioactivity was 101.0 ± 3.3% (Table 5). The plasma and renal clearances of cilastatin were similar to those of imipenem when the two drugs were given together and was not seemingly affected by coadministration of the two drugs or by imipenem-cilastatin sodium ratio.

DISCUSSION

The four volunteers in this study had previously participated in two studies of the pharmacokinetics of imipenem, which was administered alone or together with cilastatin

TABLE 6. Individual and mean urinary recovery of cilastatin after administration of cilastatin alone (treatment C) or together with imipenem[a]

Subject no.	Time (h)	Cilastatin urinary recovery[b] as determined by: HPLC			Radiometry		
		Treatment C	Treatment D	Treatment E	Treatment C	Treatment D	Treatment E
1	0–2	71.3	79.6	67.3	79.8	84.6	80.9
	2–4	7.2	8.8	8.0	11.4	16.8	16.3
	4–6	1.0	1.4	1.3	3.7	4.8	4.0
	6–10	ND[c]	ND	ND	1.7	1.6	1.8
	10–24	ND	ND	ND	0.5	0.7	0.5
	24–48	ND	ND	ND	0.1	0.1	0.1
	0–48	79.6	89.8	76.6	97.2	108.6	103.6
2	0–2	65.1	61.5	62.4	79.8	80.6	79.6
	2–4	11.1	10.6	9.8	17.3	15.7	17.7
	4–6	1.9	1.6	2.3	5.1	4.5	5.8
	6–10	ND	0.3	0.5	2.9	2.7	3.4
	10–24	ND	ND	ND	1.2	1.0	1.5
	24–48	ND	ND	ND	0.3	0.4	0.3
	0–48	78.1	74.0	75.0	106.6	104.9	108.3
3	0–2	61.0	63.9	61.9	89.9	83.1	85.0
	2–4	6.2	6.3	6.6	12.0	12.5	10.9
	4–6	0.9	0.7	0.9	3.1	2.4	2.6
	6–10	ND	ND	ND	1.7	1.2	1.2
	10–24	ND	ND	ND	0.4	0.4	0.4
	24–48	ND	ND	ND	0.1	0.1	0.1
	0–48	68.1	70.9	69.4	107.2	99.7	100.4
4	0–2	64.0	66.4	72.3	79.5	78.9	77.9
	2–4	8.4	9.7	9.2	14.2	14.0	16.7
	4–6	1.5	1.5	1.9	3.6	3.8	4.5
	6–10	0.4	ND	0.5	1.9	1.9	2.4
	10–24	ND	ND	ND	0.4	0.5	0.6
	24–48	ND	ND	ND	0.1	0.1	0.1
	0–48	74.3	77.6	83.9	99.7	99.2	102.2
1 to 4	0–2	65.4 ± 4.3[d]	67.9 ± 8.1	66.0 ± 4.9	82.3 ± 5.1	81.8 ± 2.5	80.9 ± 3.0
	2–4	8.2 ± 2.1	8.9 ± 1.9	8.4 ± 1.4	13.7 ± 2.7	14.8 ± 1.9	15.4 ± 3.1
	4–6	1.3 ± 0.5	1.3 ± 0.4	1.6 ± 0.6	3.9 ± 0.9	3.9 ± 1.1	4.2 ± 1.3
	6–10	ND	ND	ND	2.1 ± 0.6	1.9 ± 0.6	2.2 ± 0.9
	10–24	ND	ND	ND	0.6 ± 0.4	0.7 ± 0.3	0.8 ± 0.5
	24–48	ND	ND	ND	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
	0–48	75.0 ± 5.1	78.1 ± 8.3	76.2 ± 6.0	102.7 ± 5.0	103.1 ± 4.5	103.6 ± 3.4

[a] Imipenem-cilastatin ratio of 1:1 (treatment D) or 4:1 (treatment E).
[b] Percentage of dose administered.
[c] ND, Not detectable.
[d] Mean ± SD.

sodium (5; unpublished data). The kinetics of imipenem were similar in all studies; i.e., the plasma concentrations were dose proportional with an increase of the AUC when imipenem was given together with cilastatin sodium. The effects of cilastatin sodium on the plasma kinetics of imipenem was not as obvious in this study as in previous ones. However, cilastatin sodium will not increase the plasma concentrations of imipenem to an extent which could affect the therapeutic efficacy of imipenem. Also, the renal excretion pattern for imipenem was the same as that found previously in these subjects: a marked intersubject variability of the urinary recovery of active imipenem when that drug was given alone and a uniform increase of the urinary recovery to about 70% of the dose when imipenem and cilastatin sodium were coadministered. These effects of cilastatin on the urinary excretion of imipenem are likely to be of clinical importance since therapeutic levels of imipenem in urine will be maintained for a longer period with the imipenem-cilastatin sodium combination than with imipenem alone.

When ^{14}C-labeled imipenem was administered, higher levels of radioactivity than of imipenem itself were found in plasma. That finding may be explained by the observation in one of the subjects that the open lactam metabolite, which is microbiologically inactive, accounted for about 9% of the radioactivity in the samples taken immediately after treatments A and B in that subject. The mechanism(s) responsible for the systemic breakdown of the imipenem molecule is not known. Studies in animals have shown that DHP-I, which also metabolizes imipenem to the open lactam metabolite, can only be found in kidney homogenates, although other dehydropeptidases which do not metabolize imipenem are found in other tissues (2). However, similar studies on human tissues have not been reported.

The disposition of cilastatin in plasma in our subjects showed striking similarities to that of imipenem, with a half-life of about 1 h and similar AUCs, volumes of distribution, and pharmacokinetic constants. In contrast to imipenem, cilastatin seemed to undergo no or very little systemic

metabolism since the results of radiometric analysis were almost identical to those obtained by HPLC analysis. However, since urinary recovery of cilastatin and its *N*-acetyl metabolite accounted for only 88% of the cilastatin dose, whereas almost all the radioactivity was recovered in urine, further metabolism of cilastatin may occur.

Both imipenem and cilastatin were excreted by the kidneys, with fecal excretion being less than 1% of the total radioactivity for imipenem and less than 2% for cilastatin. Therefore, biliary excretion is assumed to be negligible. Also, since the renal clearance of imipenem and cilastatin exceeded the GFR in these subjects, the renal excretion of both drugs must proceed by glomerular filtration and net renal tubular secretion. This was suggested by data from previous studies, as was the probability that cilastatin acts by inhibiting the postexcretory metabolism of imipenem by blocking DHP-I (5). When imipenem alone was given to subject 2, a high metabolizer, 80 to 90% of the radioactivity in all urine samples could be ascribed to the open lactam metabolite of imipenem, the metabolite produced by DHP-I, which supported our previous findings. Additional support for our findings was provided by the observation that in subject 2, only 20% of the radioactive effluent of the sample obtained at 0 to 1 h after treatment B was representative of that metabolite, whereas the corresponding figure in the sample obtained at 4 to 6 h was 55%.

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LITERATURE CITED

1. **Calandra, G. B., F. M. Ricci, C. Wang, and K. R. Brown.** 1983. Safety and tolerance comparison of imipenem-cilastatin to cephalothin and cefazolin. J. Antimicrob. Chemother. **12**(Suppl. D):125–131.
2. **Kahan, F. M., H. Kropp, J. G. Sundelof, and J. Birnbaum.** 1983. Thienamycin: development of imipenem-cilastatin. J. Antimicrob. Chemother. **12**(Suppl. D):1–35.
3. **Kropp, H., J. G. Sundelof, R. Hajdu, and F. M. Kahan.** 1982. Metabolism of thienamycin and related carbapenem antibiotics by the renal dipeptidase, dehydropeptidase-I. Antimicrob. Agents Chemother. **22**:62–70.
4. **Kropp, H., J. G. Sundelof, J. S. Kahan, F. M. Kahan, and J. Birnbaum.** 1980. MK0787 (*N*-formimidoyl thienamycin): evaluation of in vitro and in vivo activities. Antimicrob. Agents Chemother. **17**:993–1000.
5. **Norrby, S. R., K. Alestig, B. Björnegård, L. Å. Burman, F. Ferber, J. L. Huber, K. H. Jones, F. M. Kahan, J. S. Kahan, H. Kropp, M. A. P. Meisinger, and J. G. Sundelof.** 1983. Urinary recovery of *N*-formimidoyl thienamycin (MK0787) as affected by coadministration of *N*-formimidoyl thienamycin dehydropeptidase inhibitors. Antimicrob. Agents Chemother. **23**:300–307.
6. **Norrby, S. R., K. Alestig, F. Ferber, J. L. Huber, K. H. Jones, F. M. Kahan, M. A. P. Meisinger, and J. D. Rogers.** 1983. Pharmacokinetics and tolerance of *N*-formimidoyl thienamycin (MK0787) in humans. Antimicrob. Agents Chemother. **23**:293–299.
7. **Verbist, L., and J. Verhaegen.** 1981. In vitro activity of *N*-formimidoyl thienamycin in comparison with cefotaxime, moxalactam, and ceftazidime. Antimicrob. Agents Chemother. **19**:402–406.