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Pharmacokinetics of Cefepime Dihydrochloride Arginine in Subjects with Renal Impairment

J. CRONQVIST,[1]* I. NILSSON-EHLE,[1] B. ÖQVIST,[2] AND S. R. NORRBY[1]

Departments of Infectious Diseases[1] and Nephrology,[2] University of Lund, Lund, Sweden

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In this study, the safety, tolerance, and pharmacokinetics of a single 1-g intravenous dose of cefepime (BMY-28142) were investigated. Twenty-three volunteers with various degrees of renal function were assigned to four trial groups according to glomerular filtration rates (GFR). Group IV consisted of five patients with end-stage renal disease undergoing treatment with hemodialysis. Cefepime concentrations in samples from plasma, urine, and infusion solutions were assayed with high-pressure liquid chromatography. The volume of distribution corresponded to the assumed extracellular fluid volume and did not differ significantly between the four groups. The area under the concentration-time curve increased as renal function decreased; in group II (GFR, 31 to 80 ml/[min × 1.73 m^2]; $n = 6$), it was already three times higher than in group I (GFR, ≥80 ml/[min × 1.73 m^2]; $n = 5$). Mean residence time was 2.4, 6.8, 11.4, and 31.6 h for the four groups, respectively. Total clearance decreased (97.2, 34.6, 19.8, and 6.3 ml/[min × 1.73 m^2]) with decreasing renal function, and a linear relationship between total plasma clearance and GFR was found with the regression equation $y = 0.92x - 2.0$ ($r = 0.991$). Renal clearance was linearly correlated to GFR with the regression equation $y = 0.87x - 6.1$ ($r = 0.989$), indicating that renal elimination is mainly by glomerular filtration. During hemodialysis, the extraction ratios were between 0.40 and 0.65. Dialysis clearance varied between 69.9 and 94.6 ml/(min × 1.73 m^2).

Cefepime (aminothiazolemethoxyamino cephalosporin) is a new parenteral beta-lactam antibiotic. It has a broad spectrum including activity against *Pseudomonas aeruginosa* and members of the family *Enterobacteriaceae* and retained potency against *Staphylococcus aureus* and other gram-positive organisms (5, 7, 9, 11, 17, 18). It is active against clinical isolates resistant to ceftazidime and other beta-lactams (9, 17). Cefepime is extremely stable to hydrolysis by β-lactamases (15) and penetrates well into the cerebrospinal fluid in animal models (10, 15, 16). The activity against both gram-positive and gram-negative organisms provides the possibility of empirical treatment of severe infections. Since, in patients with severe infections, renal dysfunction is common, this study was undertaken to investigate the influence of renal impairment on the pharmacokinetics of cefepime.

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* Corresponding author.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Medical Faculty, University of Lund, and by the Swedish Medical Products Agency. All subjects gave written informed consent prior to the study.

Antibiotic. Cefepime (BMY-28142) was provided by Bristol-Myers Squibb International Corporation (Wallingford, Conn.) as a dry-fill, sterile powder in vials containing 1 g of cefepime arginine dihydrochloride for reconstitution and intravenous administration. To each vial, 2.8 ml of sterile water for injection was added, giving a total volume of 4.2 ml. From two reconstituted-drug vials, 8 ml of the clear solution was withdrawn and added to 32 ml of physiological saline for injection. Exactly 20 ml of this solution was given intravenously for 5 min to each subject with a constant-rate infusion pump. The excess solution was used to fill the infusion lines and to save an aliquot for drug assay.

Volunteers. Twenty-three volunteers over 18 years of age were included in the study. Their body weights were between 50 and 110 kg, and they were in an acceptable clinical

TABLE 1. Subject characteristics for the four study groups[a]

Group (*n*)	No. of patients		Age (yrs)[b]	Wt (kg)[b]	BSA (m^2)[b]	Serum creatinine (μmol/liter)[b]	GFR (ml/[min × 1.73 m^2])[b]
	Female	Male					
I (5)	2	3	30.6 ± 5.0	74.9 ± 12.1	1.94 ± 0.24	77.2 ± 17.5	107 ± 4.1
II (6)	1	5	52.7 ± 8.2	76.0 ± 7.9	1.90 ± 0.16	169.3 ± 34.2	42.5 ± 9.9
III (7)	3	4	46.1 ± 16.8	67.6 ± 12.2	1.81 ± 0.23	352.7 ± 181.0	22.0 ± 5.8
IV (5)	3	2	41.2 ± 7.9	66.4 ± 17.3	1.77 ± 0.23	872.4 ± 212.4	ND[c]

[a] Kruskal-Wallis test results: age, $P = 0.021$; weight, $P > 0.1$; BSA, $P > 0.1$; Serum creatinine, $P < 0.001$; GFR, $P < 0.001$.
[b] Mean ± standard deviation.
[c] ND, not determined.

TABLE 2. Demographic data for the subjects in group IV

Subject	Sex[a]	Diagnosis	Yrs on dialysis	Time of cefepime administration relative to hemodialysis
19	F	Thrombotic thrombocytopenic purpura	4.5	Before
21	M	Nephrosclerosis and chronic glomerulonephritis	11	Before
22	F	Mesangioproliferative glomerulonephritis	3	Before
28	F	Chronic pyelonephritis (nephrectomy)	10	During
30	M	Chronic nephropathy	3	During

[a] F, female; M, male.

condition according to physical and laboratory examinations. Subjects were divided into four different groups on the basis of actual glomerular filtration rate (GFR) measured by iohexol clearance determination (13). Table 1 shows the characteristics of the four groups of subjects with regard to age, sex, weight, and renal function. Table 2 describes the demographic data for the subjects in group IV.

In group I, two subjects received only half the intended dose because of a miscalculation which occurred when the vials were prepared for infusion. In group II, one subject could not accurately collect urine and his urine-based data were excluded.

Exclusion criteria were pregnancy, hepatic disease, blood donation within a month prior to the investigation, known hypersensitivity to cephalosporins or penicillins, human immunodeficiency virus or hepatitis B surface antigen positivity, drug allergy, drug or alcohol abuse, and fluctuating or rapidly deteriorating renal function.

Study design. The study was an open, single-dose study with 1 g of cefepime administered intravenously for 5 min with a constant-rate infusion pump. Multiple blood samples were taken from the contralateral cubital vein predose and at 0.17, 0.34, 0.50, 0.75, 1.0, 1.5, 2, 4, 6, 8, 10, and 12 h after the start of infusion in group I. In group II, blood samples were collected as described above, with additional samples at 16, 20, and 24 h. In group III, blood samples were collected as in group II, with additional samples at 36 and 48 h after the start of infusion. In group IV, three patients were dosed 24 h before the start of hemodialysis; blood samples were collected at 0.17, 0.50, and 1 h and then every 2 h up to the start of dialysis and also at the beginning of dialysis, 0.50 h after the beginning of dialysis, and every hour thereafter. The other two patients in group IV received their dose at the start of dialysis and were monitored during dialysis with samples collected at 0.50, 1, 1.5, 2, 3, and 4 h. All patients in group IV were monitored for 2.5 h after the end of dialysis. The specific data for the dialysis procedure are shown in Tables 3 and 4. During dialysis, blood samples were taken from both the efferent and the afferent lines of the dialysis machine. Samples were centrifuged at 4°C within 60 min of collection, and plasma was separated and immediately frozen at −70°C.

Urine was collected quantitatively predose and at 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h after the start of infusion in groups I, II, and III, with additional samples taken at 12 to 24 h in groups II and III and at 24 to 36 h and 36 to 48 h in group III. The volume of each urine portion was recorded, and aliquots were mixed with 2 parts of 0.2 M sodium acetate buffer, pH 4.25, and frozen at −70°C.

Laboratory evaluation. Hematological, clinical chemical, and urinary tests were conducted predose, 8 h postdose, and at the end of the study period. GFR was measured by iohexol clearance determination (13) on the day of the study except in group IV. The iohexol dose was given immediately after the cefepime infusion.

Clinical examination. Electrocardiograms were obtained before dose administration. Physical examinations were done before and after the trial. Body temperature, blood pressure, and pulse and respiratory rates were monitored from the start of infusion and throughout the study period. Caffeine, nicotine, and alcohol were not allowed during the observation period. Subjects had a light breakfast before the start of the study and were allowed to drink freely. They were requested to report any side effects, and all observed adverse reactions were noted.

Assay procedure. Plasma and urine samples were assayed for concentrations of cefepime by high-pressure liquid chromatography using a modified version of the procedure of Barbhaiya et al. (2). A Waters ALC/GPC 204 liquid chromatograph was used with a Waters 712 WISP automatic sample injector, a Waters 450 tunable absorbance detector set at 280 nm, and a Waters data module recorder. The stationary phase consisted of a 5-μm Nucleosil C_{18} (Macherey-Nagel, Düren, Germany) slurry packed in stainless-steel columns (20 cm by 4 mm [inside diameter]). For plasma assays, the mobile phase was a mixture of 5 mM octanesulfonic acid in water and acetonitrile (90:10 [vol/vol]) with a flow rate of 1.0 ml/min. Cefepime for preparation of plasma standards was weighed precisely, dissolved in distilled water to a stock standard of 1 mg/ml, and stored at −70°C. Working standards were prepared in pooled human plasma at concentrations ranging from 1.0 to 20 mg/liter. Three milliliters of methylene chloride was mixed with 1.5 ml of acetonitrile and 5% (wt/vol) trichloroacetic acid in a glass test tube. During vortexing, 1.0 ml of plasma sample was added. This mixture was centrifuged at 2,000 × *g* for 10 min, and 10 μl of the aqueous phase was injected for chromatography. For the urine assay, cefepime was weighed precisely and dissolved in distilled water to a stock standard of 10

TABLE 3. Dialysis procedures for group IV[a]

Subject	Dialysis machine	Dialyzer	Blood flow (ml/min)	Membrane pressure (mm Hg)[b]	Membrane size (m^2)	Dialysis duration (h)
19	Gambro AK 100	Gambro GFS 12+	230	170	1.30	4
21	Gambro AK 100	Gambro F 6	200	125	1.25	5
22	Gambro AK 10	Gambro GFE 15	230	170	1.50	5
28	Gambro AK 10	Gambro GFE 18	210	120	1.80	4
30	Fresenius Bic + FCM	Gambro GFE 18	225	80	1.80	4

[a] Dialysate flow for all patients was 500 ml/min.
[b] 1 mm Hg = 133.322 Pa.

TABLE 4. Performance of the Cuprophane hollow-fiber dialyzers used[a]

Dialyzer	Thickness (μm)	In vitro clearance (ml/min) of[b]:			Ultrafiltration coefficient (ml/mm Hg/h)[c]
		Creatinine	Urea	B_{12}	
Alwall GFE 15	8	162	182	62	6.4
Alwall GFE 18	8	170	190	70	8.3
Alwall GFS 12+	8	156	180	64	6.8
Fresenius F 6	40	162	183	56	5.5

[a] Inside diameter for each was 200 μm.
[b] Perfusion flow, 200 ml/min. B_{12}, vitamin B_{12}.
[c] 1 mm Hg = 133.322 Pa.

mg/ml, and the solution was kept at −70°C. Working standards were prepared in pooled human urine at concentrations ranging from 10 to 1,000 mg/liter. One part of the standard solution was mixed with two parts of 0.2 M sodium acetate buffer, pH 4.25. The stationary phase, flow rate, detection wavelength, and injected volume were the same as for plasma. The mobile phase was a mixture of methanol, tetrahydrofuran, and 10 mM sodium dodecyl sulfate (90:15:150 [vol/vol]).

Control samples of known concentrations in pooled human plasma and pooled human urine, treated and stored in exactly the same manner as the study samples, were assayed in each series of analyses.

Pharmacokinetic analysis. Noncompartmental methods were used for calculation of pharmacokinetic variables (8). The maximum concentration of cefepime in serum (C_{max}) was defined as the concentration 5 min after the end of the cefepime infusion. The extraction ratio for cefepime during dialysis was calculated according to the formula $(C_{aff} - C_{eff})/C_{aff}$, where C_{aff} and C_{eff} are the concentrations in plasma entering and leaving the dialyzer, respectively.

The clearance of cefepime during dialysis (CL_D) was calculated as $Q_p \times [(C_{aff} - C_{eff})/C_{aff}]$, where Q_p is the plasma flow through the dialyzer, determined from the known blood flow (Q_B) and the packed-erythrocyte volume (H) according to the formula $Q_B(1 - H)$.

The area under the concentration-time curve (AUC) was calculated according to the log-trapezoidal rule and extrapolated to infinity by dividing the last measured concentration by the terminal elimination rate constant. All clearance values were corrected to a 1.73-m^2 body surface area (BSA) since the volunteers had BSAs of between 1.40 and 2.17 m^2. For the same reason, the volume of distribution at steady state (V_{SS}) was given in liters per kilogram of body weight.

Statistical moment analyses were performed, and the volumes of distribution were adjusted for infusion time. Nonrenal clearance (CL_{NR}) was calculated as the difference between total clearance (CL_T) and renal clearance (CL_R).

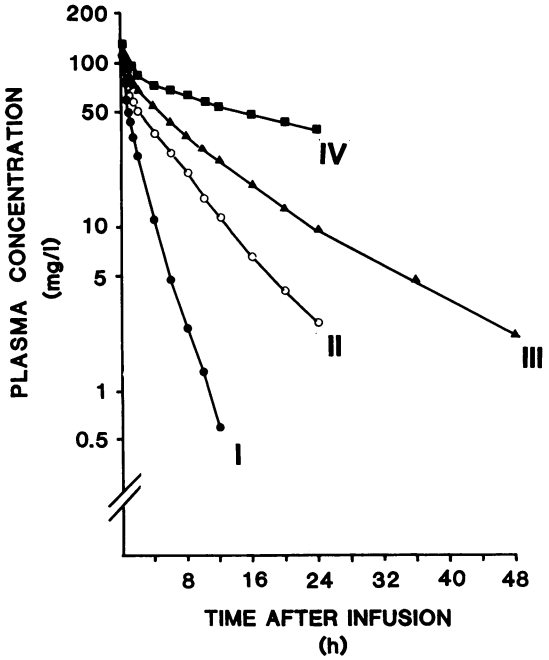

FIG. 1. Mean plasma concentration-versus-time curves for the four groups (I, healthy volunteers; II, moderate renal impairment; III, severe renal impairment; IV, end-stage renal disease) after a 1-g intravenous infusion of cefepime.

RESULTS

The mean plasma concentration-versus-time curves are shown in Fig. 1, in which the decrease in elimination with increasing renal impairment is obvious. The mean pharmacokinetic variables derived from plasma and urine data are shown in Tables 5 and 6. The V_{SS} corresponded approximately to the assumed extracellular volume and did not differ significantly among the four groups. An increase in C_{max} with progressive renal dysfunction was seen. A progressively higher AUC was noted as renal function declined. The terminal elimination half-life and the mean residence time increased with declining GFR.

The relationship between CL_T and GFR, shown in Fig. 2, was linear with the regression equation $y = 0.92\times - 2.0$ ($r = 0.991$). CL_R was linearly correlated to GFR ($y = 0.87\times - 6.1$ [$r = 0.989$]) (Fig. 3), and CL_{NR} accounted for approximately 10% of the elimination of cefepime in group I. In subjects with reduced renal function, CL_{NR} was slightly lower. In subjects with end-stage renal disease, CL_T corresponded to CL_{NR} since their renal function was virtually nonexistent.

The coefficients of variation for control plasma samples of 30 and 2 mg/liter were 4.7 and 3.8%, respectively.

TABLE 5. Plasma data-derived pharmacokinetic parameters of cefepime after a 1-g intravenous infusion[a]

Group (n)	Dose (mg)	C_{max} (mg/liter)	λ_z (h^{-1})	$t_{1/2}$ (h)	MRT (h)	AUC (mg · h/liter)	CL_T (ml/[min × 1.73 m^2])	V_{SS} (liters/kg)
I (5)	1,039 ± 26[b]	102.9 ± 22.6[b]	0.386 ± 0.0182	1.80	2.39 ± 0.09	153 ± 30[b]	97.2 ± 7.8	0.21 ± 0.03
II (6)	1,037 ± 122	114.9 ± 15.3	0.147 ± 0.0312	4.70	6.75 ± 1.56	482 ± 142	34.6 ± 9.6	0.20 ± 0.03
III (7)	1,021 ± 40	117.7 ± 21.6	0.092 ± 0.0242	7.55	11.43 ± 3.68	897 ± 257	19.8 ± 6.3	0.20 ± 0.02
IV (3)	997 ± 91	130.4 ± 23.4	0.033 ± 0.0058	21.13	31.56 ± 6.11	2,659 ± 361	6.3 ± 2.3	0.18 ± 0.06

[a] All values except $t_{1/2}$ (half-life) are means ± standard deviations. λ_z, terminal elimination rate constant; MRT, mean residence time.
[b] Two subjects were excluded after being given half the intended dose by mistake.

TABLE 6. Urine data-derived pharmacokinetic parameters of cefepime after a 1-g intravenous infusion[a]

Group (n)	CL_R (ml/[min × 1.73 m^2])	CL_{NR} (ml/[min × 1.73 m^2])	Recovery (0–12 h)	
			mg	%
I (5)	86.2 ± 8.1	11.0 ± 4.2	904.9 ± 69.9	87.7 ± 4.2
II (5)	31.9 ± 11.9	2.7 ± 2.1	822.1 ± 200.5	77.6 ± 12.7
III (7)	12.8 ± 5.6	7.0 ± 3.7	469.4 ± 142.4	45.8 ± 13.3

[a] Values are means ± standard deviations.

Urinary recoveries of the administered dose of cefepime up to 12 h postdose are shown in Table 6. The recovery in urine up to 24 h in group II was 89.6%, and the recovery up to 48 h in group III was 62.7%. The coefficients of variation for urine samples of 200 and 1,000 mg/liter were 5.2 and 4.7%, respectively.

During hemodialysis, the extraction ratio in the dialyzer was between 0.40 and 0.65. CL_D varied between 69.9 and 94.6 ml/(min × 1.73 m^2), with a mean of 83.9 ml/(min × 1.73 m^2).

Cefepime was well tolerated. Three subjects complained of mild to moderate headache, which in one instance was judged as probably related to the study drug. One subject reported a penicillin taste beginning 30 min after infusion and lasting 1 h; this was judged a drug-related reaction. Laboratory screening showed no drug-related abnormalities.

DISCUSSION

The pharmacokinetic data from this study confirm earlier published reports on patients with renal impairment (3, 4) and respiratory tract infections (12) and on healthy volunteers (1, 4, 14). Since we administered the drug as an intravenous injection for 5 min, C_{max} was higher in our group of healthy volunteers. The increase in C_{max} with decreasing renal function was probably due to reduced renal elimination rate. The lower CL_T values in this study are explained by the correction for BSA. There was no difference among V_{ss} values for the four groups. The AUC increased as renal function decreased and was already three times higher at GFR between 30 and 80 ml/min (group II) than in healthy volunteers (group I).

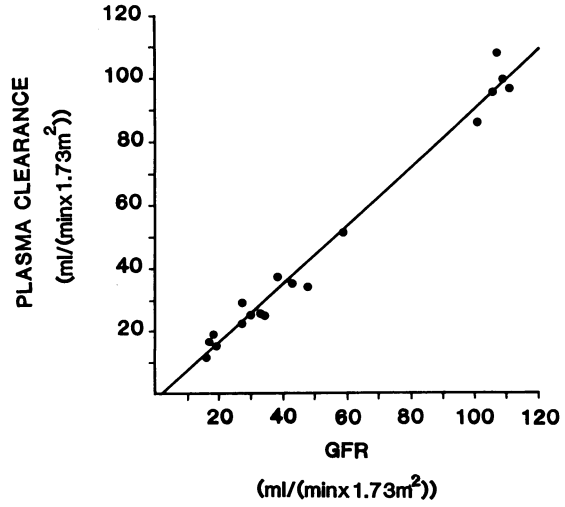

FIG. 2. Correlation between CL_T of cefepime and GFR. The correlation has the equation $y = 0.92x - 2.0$, with a correlation coefficient of 0.991.

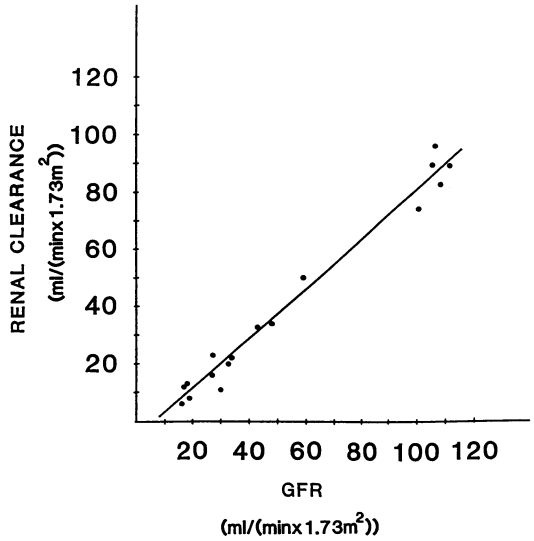

FIG. 3. Correlation between CL_R of cefepime and GFR. The correlation has the equation $y = 0.87x - 6.1$, with a correlation coefficient of 0.989.

As GFR declined, there was a proportional reduction of CL_T and a corresponding proportional reduction of CL_R. The correlation between CL_R and GFR indicates that renal elimination was mainly by glomerular filtration. CL_{NR} accounted for approximately 10% of the elimination of cefepime in healthy volunteers, which is comparable to data reported earlier (1–4). The metabolic clearance of cefepime is assumed to take place in the liver by hydrolysis to *N*-methylpyrrolidine, an alicyclic tertiary amine, and further oxidation to *N*-methylpyrrolidine-*N*-oxide (6). The three patients with end-stage renal disease who were dosed 24 h before the start of dialysis had an average CL_T of 6.3 ml/(min × 1.73 m^2), which, since the patients were anuric, corresponded to the CL_{NR} and was not different from the CL_{NR} values for the other three groups. Thus, no evidence of compensation by increased metabolic clearance was found in patients with renal insufficiency.

The data obtained in this investigation, with a linearity between GFR and CL_T, indicate that it is advisable to base dosing recommendations on renal function. Our data support the recommendation of the manufacturer for a dose reduction of cefepime for patients with severe renal insufficiency. A proposed dosing schedule for cefepime is presented in Table 7.

Hemodialysis effectively cleared cefepime from the circulation. CL_D averaged 83.9 ml/(min × 1.73 m^2), which is

TABLE 7. Suggested dosages for patients with renal impairment

Creatinine clearance (ml/min)	Dose (mg)	Interval (h)
>30	1,000	12
<30	500	24
<10	250	24[a]

[a] Supplementary dose after hemodialysis.

comparable to the CL_T for the healthy volunteers in group I. The half-life during dialysis was 1.94 h, which is close to the half-life of 1.80 h obtained for healthy subjects. A supplementary dose of 250 mg is recommended after hemodialysis.

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