Pharmacokinetics of Cefepime in Patients with Respiratory Tract Infections

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The steady-state pharmacokinetics of cefepime were evaluated in 10 middle-aged and elderly patients with acute lower respiratory tract infections who were receiving 1 g intravenously every 12 h. One preinfusion and 15 postinfusion serum samples and total urine output were collected over one dosing interval between days 3 and 8 of therapy. Cefepime concentrations in serum over time exhibited a multicompartmental profile. Peak and trough concentrations in serum determined by a validated high-performance liquid chromatography method were 71.2 ± 17.2 (mean ± standard deviation) and 6.0 ± 4.9 mg/liter, respectively. The steady-state volume of distribution was 0.22 ± 0.05 liter/kg. Elimination half-lives ranged from 1.93 to 6.04 h (3.92 ± 1.28 h), and total body clearances ranged from 36.9 to 102 ml/min per 1.73 m² (73.0 ± 19.7 ml/min per 1.73 m²). The disposition of cefepime at steady state in patients was comparable to previous observations in healthy elderly volunteers. The predictive performance of regression equations derived from single-dose studies in volunteers relating creatinine clearance with total body and renal clearances of cefepime exhibited slight biases (mean predictive errors, −9.7 and 2.1 ml/min per 1.73 m², respectively) and similar precisions. Predicted and observed total body clearances (63.3 ± 25.1 versus 73.0 ± 19.7 ml/min per 1.73 m², respectively) and renal clearances (51.3 ± 24.4 versus 49.3 ± 19.6 ml/min per 1.73 m², respectively) were not significantly different. The pharmacokinetics of cefepime in infected patients appeared to be unaltered by illness, and the steady-state disposition of cefepime was predictable from data derived from single-dose studies in volunteers.

Cefepime is an investigational cephalosporin which, in comparison with currently marketed extended-spectrum agents, demonstrates increased coverage against gram-positive organisms while retaining a broad spectrum of activity against gram-negative organisms. Against members of the family Enterobacteriaceae, MICs for 90% of strains are generally ≤0.5 mg/liter, against Pseudomonas aeruginosa they are ≤8 mg/liter, and against Staphylococcus aureus they are ≤4 mg/liter (6, 15, 16). In healthy adult volunteers, cefepime exhibited a multicompartmental serum concentration-versus-time profile with an elimination half-life ($t_{1/2\beta}$) of approximately 2 h (14). The pharmacokinetic disposition of cefepime has also been characterized in healthy elderly volunteers after single-dose intravenous administration. Elderly subjects had higher concentrations of drug in serum throughout the sampling period, with a prolonged $t_{1/2\beta}$ and decreased systemic clearance primarily because of age-related decreases in renal function (R. H. Barbhaiya, C. A. Knupp, K. A. Pittman, J. Tenny, and R. R. Martin, Proc. 16th Int. Congr. Chemother., p. 307, 1989). Consistent with the fact that renal clearance (CL_R) represents the primary route of cefepime elimination, creatinine clearance (CL_{CR}), systemic cefepime clearance (CL), and CL_R are highly correlated (S. T. Forgue, D. R. P. Guay, E. A. Morgenthein, G. R. Matzke, and R. H. Barbhaiya, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 129, 1988).

While those investigations involved noninfected volunteers who were evaluated following single-dose administra-

tion, the ultimate recipients of an intravenous antibiotic are hospitalized patients who receive maintenance-dose therapy for the treatment of infections. Pharmacokinetic parameters derived from single-dose studies, however, do not always accurately predict multiple-dose disposition (8). Moreover, the presence of an acute infection itself has been identified by some investigators as a factor which can significantly alter the pharmacokinetics of antibiotics (5, 7, 12). Such an effect has not, however, been consistently observed (3, 9–11). Inasmuch as the pharmacokinetics of cefepime have not been evaluated during maintenance-dose administration in older subjects or in patients with acute illnesses, this study was designed to characterize its disposition at steady state in middle-aged and elderly hospitalized patients being treated for respiratory tract infections. Furthermore, the accuracy with which the steady-state pharmacokinetics of cefepime in patients could be predicted from the relationships between CL_{CR} and cefepime CL and CL_R derived from studies in noninfected volunteers was assessed.

MATERIALS AND METHODS

Patients. Patients who were moderately to severely ill with lower respiratory tract infections were enrolled in the study. Subjects were excluded if they had a known allergy to cephalosporins or had impairment of renal function (serum creatinine level, >2.1 mg/dl) or hepatic function (alanine aminotransferase, aspartate aminotransferase, or bilirubin greater than twice the upper limit of normal). All patients received cefepime under a clinical efficacy and safety investigational protocol approved by the Medical Ethics Committees of the University Hospital Utrecht and the Lichtenberg Hospital, Amersfoort, The Netherlands. Informed consent

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was granted by the patients or their legal guardians prior to enrollment in the study.

Study design. A medical history, physical examination, and laboratory screening profile (hematology, serum chemistry, and urinalysis) were completed for each patient before participation in the study, on the day of the pharmacokinetic assessment, and after the conclusion of therapy.

Cefepime was supplied by Bristol-Myers Co., Brussels, Belgium. Each subject received 1 g of cefepime diluted in 0.9% sodium chloride and infused into a forearm vein over a 30-min period every 12 h. On one occasion between days 3 and 8 of therapy (day 5.5 ± 1.7), multiple blood samples (5 ml) were collected via an indwelling heparin catheter located in a forearm vein of the arm contralateral to that used for drug administration. Samples were withdrawn into siliconized glass tubes without additives (Becton Deckinson Vacutainer Systems, Rutherford, N.J.) prior to administration; 10, 20, and 30 min during infusion; and 5, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 11.5 h after the end of the infusion. Blood was allowed to clot at room temperature, and serum was separated by centrifugation and frozen at $-20°C$ until it was assayed. Urine was collected prior to and at intervals of 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h after the beginning of the infusion. After quantitation, a portion of each urine collection was stored at $-20°C$ until it was assayed.

Chemical analysis. The concentration of cefepime in serum and urine was determined by a reverse-phase high-performance liquid chromatographic assay modified from Barbhaiya et al. (1). Separation of cefepime from cefadroxil (serum internal standard) or cephradine (urine internal standard) was achieved by using a C_{18} reversed-phase column (LiChroCART 250-4; particle size, 5 μm; 4.0 by 250 mm; E. Merck AG, Darmstadt, Federal Republic of Germany) and UV detection (254-nm wavelength for the serum assay, 280-nm wavelength for the urine assay). The serum mobile phase consisted of acetonitrile–0.005 M octane sulfonic acid (14:86) at a flow rate of 1.0 ml/min. The composition of the urine mobile phase was methanol–0.01 M sodium dodecyl sulfate–5% (wt/vol) trichloroacetic acid–0.85 M phosphoric acid–tetrahydrofuran (49.7:40.4:9:0.7:5.3) at a flow rate of

2.0 ml/min. Retention times of cefepime and internal standard in the serum assay were 8.2 and 20 min, respectively, and in the urine assay they were 12 and 15 min, respectively. The minimum detectable concentration was 0.5 mg/liter in serum and 2.5 mg/liter in urine. No chromatographic interference from theophylline and a variety of other drugs was observed. The intra- and interassay coefficients of variation were less than 14% for low (1 mg/liter) and 4% for high (50 mg/liter) cefepime standards in serum and less than 11% for low (10 mg/liter) and 3% for high (500 mg/liter) cefepime standards in urine which were prepared in our laboratory.

Data analysis. The elimination rate constant (β) of the log-linear terminal portion of the cefepime serum concentration-versus-time curve (times, 5 to 11.5 h after the infusion) was determined by nonlinear regression analysis with weighting of $1/y^2$. $t_{1/2β}$ was calculated as ln $2/β$. CL, CL_R, and volume of distribution at steady state (V_{ss}) were calculated from the following equations: $CL = dose/AUC$; $CL_R = (A)(V)/AUC$; and $V_{ss} = (MRT - T/2) CL$. In these equations, dose is the intravenous cefepime administered; AUC is the area under the concentration-time curve over the dosing interval from 0 to 12 h at steady state obtained by the trapezoidal rule; A is the concentration of cefepime excreted unchanged in urine; V is the volume of urine, and T is infusion duration. Mean residence time (MRT) was calculated by the method of Bauer and Gibaldi (2), and nonrenal clearance (CL_{NR}) was determined as the difference between CL and CL_R.

The predictive performance of the relationships between CL_{CR} and cefepime CL and CL_R in noninfected volunteers (Forgue et al., 28th ICAAC) was assessed. Cefepime clearances were calculated for each patient by the equations $CL = 0.96 CL_{CR} + 10.92$ and $CL_R = 0.88 CL_{CR} + 0.33$, where CL_{CR} was estimated by the formula of Cockroft and Gualt (4).

The paired student t test and orthogonal regression analysis were used to compare the observed and predicted cefepime CLs and CL_Rs. Mean predictive error was used as a measure of bias, and root mean squared error was used as a measure of precision. These were calculated as mean predictive error = $(\Sigma\ pe)/n$ and root mean squared error =

TABLE 1. Demographic characteristics of study patients

Patient no.	Sex[a]	Age (yr)	Wt (kg)	Ht (cm)	CL_{CR} (ml/min per 1.73 m²)[b]	Infection type[c]	Relevant medical history[d]	Concomitant medications
1	F	62	67.9	152	36.7	P, B	COPD, diabetes mellitus, chronic cardiac failure	Theophylline, prednisone, insulin, furosemide, captopril
2	F	79	77.0	163	61.6	B	COPD, hypertension, diverticulosis, pyelitis	Theophylline, prednisone, furosemide, temazepam
3	M	71	62.9	175	45.4	B	COPD, hypertension, gastritis, arthritis, cardiac decompensation	Theophylline, prednisone, enalapril, triamterene, amiloride
4	M	60	58.0	176	65.2	B	COPD, atrial hypertrophy	Furosemide
5	F	98	50.5	162	27.9	P	Hypertension, cardiac decompensation	Theophylline, digoxin, furosemide, hydralazine, hydrocortisone
6	M	74	59.4	163	57.5	P	COPD, diabetes mellitus, intermittent claudication	Theophylline, prednisone, insulin, furosemide, digoxin
7	M	71	66.0	182	53.8	P	Atrial fibrillation, dementia	Haloperidol, trimeprazine
8	F	50	84.7	163	120	P	COPD, atrial fibrillation	Prednisone
9	M	89	50.8	178	31.8	P	COPD, dementia	Theophylline, furosemide, flecainide, nitrazepam
10	M	79	75.0	169	45.5	P	Lung carcinoma	Dipyridamole

[a] F, Female; M, male.
[b] CL_{CR} estimated by the formula of Cockroft and Gault (4).
[c] P, Pneumonia; B, acute exacerbation of chronic bronchitis.
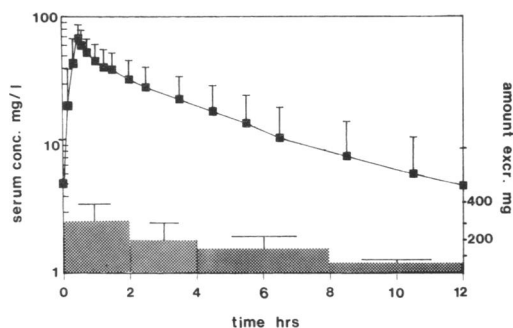[d] COPD, Chronic obstructive pulmonary disease.

FIG. 1. Serum concentration-time curve (■) and urinary excretion (histogram) of cefepime in patients ($n = 10$) during maintenance dose intravenous administration. Data are means ± standard deviations.

$\sqrt{[\Sigma(pe^2)/n]}$, where pe = predicted clearance − observed clearance and n is the number of paired clearances. Statistical significance was assumed at $P < 0.05$. Data are presented as mean ± standard deviation.

RESULTS

The demographic characteristics of study participants are documented in Table 1. Subjects ranged in age from 50 to 98 years (mean age, 73 ± 14 years) and had a mean weight of 65.2 ± 11.2 kg. Patients were hospitalized with moderate to severe lower respiratory tract infections, including pneumonia and acute exacerbation of chronic bronchitis. The maximum temperature was 37.9 ± 1.1°C, and the mean pretherapy leukocyte count was $(11.3 \pm 5.4) \times 10^3/\text{mm}^3$. The duration of cefepime therapy was 10 ± 2 days and was well tolerated by all subjects. No adverse events or laboratory abnormalities attributed to the drug were observed. An episode of mild phlebitis at the site of infusion after 7 days of therapy occurred in one patient.

A semilogarithmic plot of the cefepime serum concentration-versus-time data was multicompartmental for all patients (Fig. 1). The corresponding pharmacokinetic parameters are displayed in Table 2. Following a 1-g dose, the mean peak cefepime concentration in serum at the end of the infusion was 71.2 ± 17.2 mg/liter, and the mean trough concentration 11.5 h after the end of the infusion was 6.0 ± 4.9 mg/liter. $t_{1/2\beta}$ ranged from 1.93 to 6.04 h (3.92 ± 1.28 h), and V_{ss} ranged from 0.15 to 0.29 liter/kg (0.22 ± 0.05

liter/kg). Mean CL, CL_R, and CL_{NR} were 73.0 ± 19.7, 49.3 ± 19.6, and 24.0 ± 8.84 ml/min per 1.73 m², respectively. Over the 12-h dosing interval, 65.3% ± 14.9% of the dose was excreted unchanged in the urine. The mean amount of cefepime excreted during each period of the fractional urine collection is shown in Fig. 1.

The clearance regression equations exhibited minor mean predictive errors of −9.7 and 2.1 ml/min per 1.73 m² for CL and CL_R, respectively, and similar root mean squared errors of 19.5 and 17.3 ml/min per 1.73 m², respectively. No significant differences were noted between mean predicted and observed CLs (63.3 ± 25.1 versus 73.0 ± 19.7 ml/min per 1.73 m², respectively) or CL_Rs (51.3 ± 24.4 versus 49.3 ± 19.6 ml/min per 1.73 m², respectively). Furthermore, predicted and observed clearances were significantly correlated: for CL, $r = 0.7088$ and $P < 0.01$; for CL_R, $r = 0.6706$ and $P < 0.05$.

DISCUSSION

The disposition of cefepime in healthy elderly volunteers has been reported to differ significantly from that in young adults (Barbhaiya et al., 16th Int. Congr. Chemother.). Specifically, elderly subjects exhibited larger volumes of distribution, prolonged $t_{1/2\beta}$s, and decreased systemic clearances. These age-related changes in pharmacokinetic parameters were attributed primarily to decreases in renal function in elderly individuals. In the present investigation, mean pharmacokinetic parameters evaluated at steady state in older patients being treated for acute infections compared favorably with those of elderly, noninfected volunteers. CLs in female and male patients were 1.18 and 1.09 ml/min per kg, respectively, compared with 1.21 and 1.11 ml/min per kg in elderly female and male volunteers, respectively. When normalized to body weight, volumes of distribution were identical in female and male patients (0.22 liter/kg) and were similar to values derived from healthy elderly females (0.24 liter/kg) and males (0.23 liter/kg). While no gender differences in $t_{1/2\beta}$ were noted in elderly volunteers (3.05 versus 2.92 h in females and males, respectively), male patients exhibited slightly longer $t_{1/2\beta}$s (4.40 ± 1.29 h) than those of female patients (3.19 ± 0.98 h). This difference was not statistically significant but consistent with the lower CL_{CR}s observed in this group of male patients (49.9 versus 61.6 ml/min per 1.73 m² for males and females, respectively).

The variance in pharmacokinetic parameters (area under the concentration-time curve, $t_{1/2\beta}$, and clearances) was

TABLE 2. Steady-state pharmacokinetic parameters of cefepime in patients[a]

Patient no.	C_{max} (mg/liter)	$t_{1/2\beta}$ (h)	AUC (mg · h/liter)	MRT (h)	V_{ss} (liter/kg)	CL (ml/min per 1.73 m²)	CL_R (ml/min per 1.73 m²)	CL_{NR} (ml/min per 1.73 m²)	Ae (mg)
1	41.4	3.80	232	4.33	0.26	75.3	35.4	39.9	470
2	61.8	2.92	173	3.30	0.23	91.1	63.8	27.3	700
3	81.3	6.04	208	3.01	0.21	78.3	61.6	16.7	786
4	68.5	4.01	241	3.24	0.21	70.0	49.3	20.7	705
5	89.8	4.10	310	3.97	0.24	61.2			
6	85.1	2.76	208	3.22	0.24	84.5	65.7	18.8	777
7	47.3	3.61	189	3.82	0.29	82.5			
8	89.8	1.93	149	2.17	0.15	102	69.6	32.4	683
9	66.2	5.83	480	4.72	0.19	36.9	13.8	23.1	374
10	80.8	4.17	323	3.90	0.15	48.0	35.0	13.0	730
Mean ± SD	71.2 ± 17.2	3.92 ± 1.28	251 ± 97.5	3.57 ± 0.73	0.22 ± 0.05	73.0 ± 19.7	49.3 ± 19.6	24.0 ± 8.84	653 ± 149

[a] Abbreviations: C_{max}, maximum concentration of cefepime in serum; $t_{1/2\beta}$, elimination half-life; AUC, area under the concentration-time curve; MRT, mean residence time; V_{ss}, volume of distribution at steady state; CL, systemic clearance; CL_R, renal clearance; CL_{NR}, nonrenal clearance; Ae, amount of cefepime excreted unchanged in urine over 12-h dosing interval.

greater in this patient population than it was in elderly volunteers. While these patients are representative of those treated on our pulmonary ward, they were nonetheless heterogeneous in terms of infection type, severity of infection, and concurrent disease states. A variety of concomitant medications was administered during the course of cefepime therapy (Table 1), some of which, such as diuretics, may influence the disposition of antibiotics. These factors or a combination of them may have contributed to the observed variabilities. Additionally, the range of $CL_{CR}s$ measured in this patient group was broader than those measured in elderly subjects in the volunteer study of Barbhaiya et al. (16th Int. Congr. Chemother.). Inasmuch as cefepime is primarily eliminated unchanged in the urine, variability in renal function most likely represents the primary factor accounting for the increased kinetic variance that was observed. Similar findings have been reported for other antibiotics in elderly patients [11].

The regression equations relating renal function with cefepime CL and CL_R derived from single-dose studies in volunteers performed well in predicting steady-state clearances in patients. A small negative bias was observed for the CL equation, and a slight positive bias was observed for the CL_R equation; both, however, were less than 10 ml/min per 1.73 m^2. The equations demonstrated similar precision of approximately 20 ml/min per 1.73 m^2. These relationships would therefore be useful in the clinical setting as the basis for dosage adjustment [13] for patients with impaired renal function who are receiving cefepime.

The results of this investigation suggest that the pharmacokinetics of cefepime during maintenance-dose therapy in middle-aged to elderly, hospitalized patients are consistent with values projected from single-dose investigations. Furthermore, acute illness does not appear to alter the disposition of cefepime significantly. Relationships between renal function indices and cefepime clearances derived from noninfected volunteers perform well in predicting the cefepime disposition during multiple-dose administration in infected patients.

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