ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1990, p. 1118–1122
0066-4804/90/061118-05$02.00/0

Vol. 34, No. 6

Safety, Tolerance, and Pharmacokinetic Evaluation of Cefepime after Administration of Single Intravenous Doses

R. H. BARBHAIYA,[1]* S. T. FORGUE,[1] C. R. GLEASON,[1] C. A. KNUPP,[1] K. A. PITTMAN,[1] D. J. WEIDLER,[2] AND R. R. MARTIN[3]

Department of Metabolism and Pharmacokinetics, Pharmaceutical Research and Development Division, Bristol-Myers Squibb Company, P.O. Box 4755, Syracuse, New York 13221-4755[1]; Center for Advanced Therapeutics and Clinical Research, Department of Medicine, University of Miami School of Medicine, Miami, Florida 33101[2]; and Department of Infectious Diseases Clinical Research, Pharmaceutical Research and Development Division, Bristol-Myers Squibb Company, Wallingford, Connecticut 06492[3]

Received 3 November 1989/Accepted 13 March 1990

In this double-blind, single-dose phase I study, the safety and tolerance of cefepime were assessed in 24 healthy male subjects, with ceftazidime as the control drug. Four subjects in each of the six dose groups (62.5, 125, 250, 500, 1,000, or 2,000 mg as a 30-min intravenous infusion) received each antibiotic, according to a crossover design, with a 2-day washout period between treatments. Blood and urine samples were obtained to characterize the pharmacokinetics of cefepime. Plasma and urine samples were assayed for intact cefepime. Samples containing ceftazidime were discarded. The adverse effects observed in the study were mild and infrequent, with prompt recovery from adverse experiences and abnormal laboratory values. The cefepime pharmacokinetic parameters for the therapeutically significant doses of 250 to 2,000 mg appeared to be proportional to dose and similar to literature values for ceftazidime. The elimination half-life of about 2 h was independent of the dose. Urinary recovery of intact cefepime was invariant with respect to dose; an overall mean value of 82% of dose was obtained for the four highest levels. Mean renal clearance was 105 ml/min and suggestive of glomerular filtration as the primary excretion mechanism. In normal humans, the safety and pharmacokinetic profiles of cefepime are very similar to those of ceftazidime.

Cefepime (BMY-28142; Bristol-Myers Squibb Co.) is a "fourth-generation" cephalosporin antibiotic with significant potential advantages over other broad-spectrum cephalosporins and some nontraditional beta-lactam antibiotics (4, 9, 18). It differs from other aminothiazolyl methoxyimino cephalosporins by having a quaternized *N*-methyl pyrrolidine moiety attached to the methylene group at C-3 (Fig. 1). In addition to a very broad antimicrobial spectrum, cefepime appears to have low affinity for major chromosomally mediated β-lactamases and thus is less affected by the nonhydrolytic barrier mechanism of resistance in these bacteria (14). These in vitro advantages have been borne out in a number of in vivo infection models (9, 17).

Preclinical safety evaluation and pharmacokinetic studies of cefepime were done primarily with rats and monkeys. The findings of these studies suggest that when administered by intravenous infusion, cefepime is as safe as other commercially available cephalosporins. The pharmacokinetics in rats and monkeys have been extensively characterized (2, 7). The present phase I study was designed to evaluate the safety, tolerance, and pharmacokinetics of cefepime in healthy male volunteers.

MATERIALS AND METHODS

Study design. The purposes of this study were to evaluate the safety and tolerance of cefepime after single intravenous doses of 62.5, 125, 250, 500, 1,000, and 2,000 mg to normal human volunteers. The pharmacokinetics of cefepime were also assessed at each dose level. The study was conducted in a randomized, double-blind manner, with ceftazidime (Fortaz; Glaxo Pharmaceuticals, Ltd.) as the control drug. Each of four subjects in each of the six dose groups received a 30-min infusion of each antibiotic, according to a crossover design, with a 2-day washout period between treatments. The safety evaluation included vital signs, electrocardiogram, phonocardiography, and routine laboratory tests. Blood and urine samples were collected for pharmacokinetic assessment.

Subjects. A total of 24 healthy male volunteers participated after having signed an informed consent form. The subjects had a mean (± standard deviation [SD]) age of 28.5 (±5) years, a mean body weight of 84.6 (±8.6) kg, and a mean height of 184 (±7.6) cm. Subject exclusion criteria included the presence of drug allergies or intolerance and a history of drug or alcohol abuse. Use of any medications within 2 weeks and use of alcohol within 24 h of induction into the study were not permitted. Use of any drug, including alcohol and caffeine, during the study course was forbidden. The subjects were instructed to refrain from smoking during blood and urine sampling periods. Confinement to the test facility began the day before the subject received his first dose and continued until his release from the study. Each subject fasted from 2200 h on the day preceding dosing until a standardized lunch was served about 3 h after dosing. To ensure adequate diuresis for urine sampling, subjects drank 200 ml of water or juice 1 h prior to the infusion and approximately 1, 2, and 3 h after the start of dosing.

Drug formulation and administration. The test drug, cefepime, was supplied in vials containing a lyophilized mixture with sodium chloride, 575 mg of cefepime activity per vial. Reconstitution of each vial with 1.9 ml of sterile water for injection provided 2.3 ml of a 250-mg/ml solution of dipolar ionic cefepime. The reconstituted solution was diluted with sufficient sterile water to prepare infusion solu-

* Corresponding author.

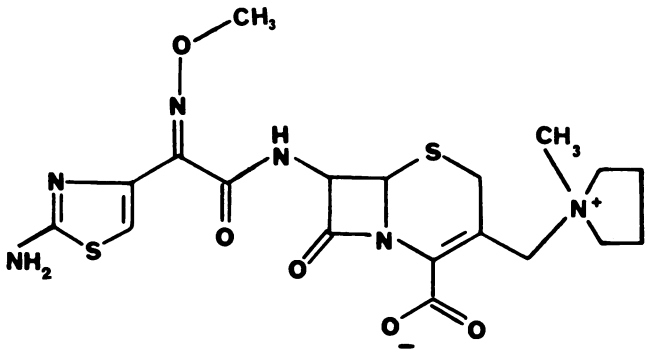

FIG. 1. Structure of cefepime, pyrrolidinium 1-((7-(((2-amino-4-thiazolyl)(methoxyimino)-acetyl)amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo(4.2.0)oct-2-en-3-yl)methyl)-1-methyl-, hydroxide, inner salt, (6*r*-(6 · α,7 · β · *z*))-.

tions of 1.25, 2.5, 5.0, 10.0, 20.0, and 40.0 mg of cefepime per ml for doses of 62.5, 125, 250, 500, 1,000, and 2,000 mg, respectively. Ceftazidime solutions were prepared in the same manner, except that 500-mg vials were reconstituted with 5.0 ml of sterile water, providing a reconstituted solution of 100 mg/ml. This solution was subsequently diluted to form the same infusion solution concentrations as noted above for cefepime.

Each cefepime and ceftazidime dose was administered as a constant-rate infusion by using an Autosyringe Model AS58 infusion pump calibrated to deliver 50 ml of infusion solution in the 30-min infusion interval. Administration was via a forearm vein contralateral to that used for blood sampling.

Safety evaluation. Blood pressure readings were obtained from each subject on admission to the study, prior to dosing, and every 3 min during infusion. Additional readings were obtained as follows: every 15 min from 0.75 to 1.5 h, every 30 min from 2 to 2.5 h, and every 4 h up to 24 h after initiation of the infusion. Pulse rates were monitored by electrocardiogram until 2 h postinfusion. Subsequently, pulse rates were determined manually and recorded at 4 and 6 h and every 4 h until 24 h postinfusion. Temperature and respiration were taken predose and at the end of each infusion.

Phonocardiography was performed to monitor for possible alterations in pressure-flow relationships across the pulmonary valve during infusion. Phonocardiograms were obtained around the time of dosing at the following intervals: preinfusion; during infusion at 5, 10, 15, 20, 25, and 30 min (end of infusion); and at 1, 4, and 24 h.

Routine laboratory tests were performed on each subject within 2 weeks prior to the first treatment session. Tests were repeated within approximately 24 h prior to dosing and again 24 h after dosing.

Collection and analysis of blood and urine samples. Blood samples were drawn from each subject at the following times after the beginning of the infusion: predose, 30 min (end of infusion), and 2, 4, 6, and 8 h. Each heparinized blood sample was centrifuged to prepare plasma, 2.5 ml of which was transferred to a 10- to 15-ml screw-cap polypropylene tube and frozen (−20°C) within 2 h of collection. The total urine output of each subject was collected as discrete samples for each of the following intervals: predose and 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 16 h postdose. At the end of each interval, the total urine sample was thoroughly mixed and total volume and pH were recorded. A 3.0-ml portion of urine was transferred to a 15-ml polypropylene tube containing 6.0 ml of 0.2 M sodium acetate buffer, pH 4.25, and stored at −20°C.

Plasma and urine samples were analyzed for intact cefepime by validated high-pressure liquid chromatography assays (2). All samples containing ceftazidime were discarded without analysis.

Pharmacokinetic analysis. Plasma cefepime concentration (C)-versus-time (t) data for each subject were evaluated by noncompartmental methods. The highest observed C, which occurred at the end of infusion, was defined as C_{max}. Elimination half-life ($t_{1/2}$) was calculated as $(\ln 2)/b$, where b was the absolute value of the slope of the least-squares regression line for n terminal datum points. These datum points ($n \geq 3$) were selected to minimize the mean-square error term from the regression. The predicted value of C at the last sampling time, t', was C'. The area under the C-versus-t curve (AUC) and the area under the first moment of the C-t curve (AUMC) were estimated by the trapezoidal and log-trapezoidal methods. The terms C'/b and $(C'/b)(t' + 1/b)$ were added to AUC and AUMC values, respectively, for extrapolation to infinite time. Mean residence time in the body was estimated as $AUMC_{0-\infty}/AUC_{0-\infty} - T/2$, where $AUMC_{0-\infty}$ and $AUC_{0-\infty}$ are AUMC and AUC from 0 h to infinity, respectively, and the infusion time (T) was 0.50 h. Total body clearance (CL_T) was calculated as dose/$AUC_{0-\infty}$.

Estimation of $t_{1/2}$ from the regression analysis of the amount of cefepime remaining to be excreted at the end of each urine collection interval was also accomplished as described by Ritschel (16). Terminal points ($n \geq 3$) used to define the log-linear phase regression were chosen to minimize the mean-square error term in a manner analogous to that employed in the plasma data evaluation. Renal clearance (CL_R) was calculated as $X_u/AUC_{0-\infty}$, where X_u is the amount of intact cefepime excreted in urine. The percent of dose recovered in urine ($\%X_u$) was calculated as X_u/dose × 100.

Statistical analysis. Weighted regression analyses were performed to evaluate C_{max} (at the end of the infusion) versus dose and $AUC_{0-\infty}$ versus dose. Reciprocal variance estimates at each dose level were used as weights. The 95% confidence limits around the slope and intercept estimates were used to test the significance of the regression. A lack-of-fit component was added to the linear model to test for departure from linearity.

$\%X_u$, CL_R, CL_T, and $t_{1/2}$ were evaluated for each dose by using a one-way analysis of variance model followed by the Tukey multiple comparison procedure. A log transformation of urinary excretion data was applied to the data to reduce the skewness. Hypotheses were tested at the 5% significance level.

RESULTS

Safety and tolerance. Thirteen of the twenty-four subjects had no complaints during or following infusion of either cephalosporin. The other 11 volunteers had minor complaints which were randomly distributed between periods of cefepime and ceftazidime therapy. One subject noted coldness and/or numbness of the arm during infusion of each drug. Another subject experienced urinary urgency with each infusion, probably related to forced diuresis. Four episodes of lightheadedness and two headaches occurred, along with one episode of each of the following: coughing, sore neck, substernal sensation of being hot, flatulence, diaphoretic hand, and a heavy feeling in the arm.

No abnormalities were noted in vital signs, electrocardio-

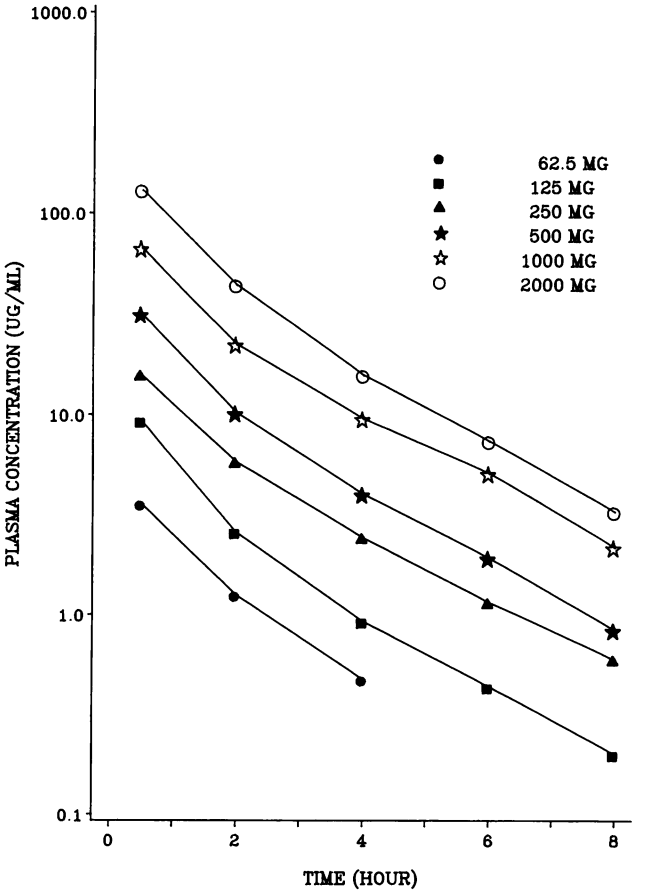

FIG. 2. Mean plasma concentration-versus-time profiles of cefepime after administration of intravenous doses.

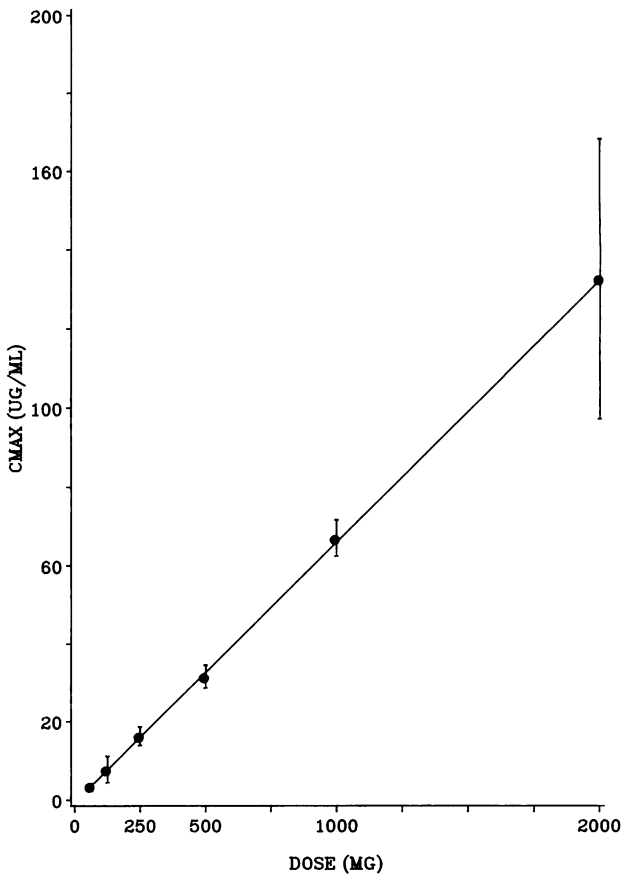

FIG. 3. Linear regression evaluation of C_{max} and cefepime dose ($r = 0.99$; $C_{max} = -0.56 + 0.066 \cdot$ dose).

grams, or phonocardiograms. Two patients had slight (1.5 to 2 times normal) liver transaminase elevations within 48 h of the second infusion, which returned to the normal range within a few days. Because both cefepime and ceftazidime had been administered, a specific drug could not be implicated.

Pharmacokinetics. To ensure that blood sampling, an invasive procedure, for pharmacokinetic assessment did not compromise safety and tolerance assessment, the number of blood samples collected was limited to that essential for baseline pharmacokinetic evaluation. Mean cefepime plasma concentration-versus-time profiles, which are representative of individual data, for each dose level are shown in Fig. 2. The combination of limited plasma sampling and relatively low cefepime levels renders the accuracy of parameter estimates for the two lowest dose groups equivocal. For example, the short apparent $t_{1/2}$s are invariably artifacts arising from an inadequate number of datum points in the terminal elimination phase. These two dose groups were incorporated into the study essentially for reasons of safety and tolerance assessment. The lowest therapeutic dose is projected to be 250 mg, and hence estimates of pharmacokinetic parameters for doses of 62.5 and 125 mg are of secondary interest.

The mean (±SD) pharmacokinetic parameters for cefepime are shown in Table 1. The mean C_{max} values ranged from 3.6 to 133 μg/ml for the 62.5- and 2,000-mg doses, respectively. Statistical evaluation of C_{max} confirmed that it was proportional to dose (Fig. 3). The $AUC_{0-\infty}$ also

TABLE 1. Pharmacokinetic parameters of cefepime after administration of intravenous doses[a]

Dose (mg)	C_{max} (μg/ml)[b]	MRT (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg · h/ml)	CL_T (ml/min)	CL_R (ml/min)	$\%X_u$
62.5	3.6 ± 0.6	1.9 ± 0.5	1.3 ± 0.4	7 ± 2	155 ± 38	117 ± 35	75.3 ± 14.0
125	9.3 ± 1.6	2.2 ± 0.7	1.6 ± 0.3	14 ± 3	153 ± 37	138 ± 47	88.6 ± 10.3
250	16.3 ± 2.4	2.3 ± 0.3	1.9 ± 0.2	34 ± 3	122 ± 10	96 ± 19	78.4 ± 11.3
500	31.6 ± 2.9	2.0 ± 0.1	1.8 ± 0.2	62 ± 6	136 ± 13	116 ± 11	85.6 ± 2.9
1,000	66.9 ± 4.6	2.2 ± 0.1	1.9 ± 0.2	137 ± 9	122 ± 8	103 ± 5	84.2 ± 2.2
2,000	133 ± 35.5	1.9 ± 0.4	1.8 ± 0.2	263 ± 33	128 ± 16	104 ± 12	81.3 ± 6.9

[a] Values are means ± SD. MRT, Mean residence time. Other abbreviations are defined in the text.
[b] Data at the end of a 30-min infusion.

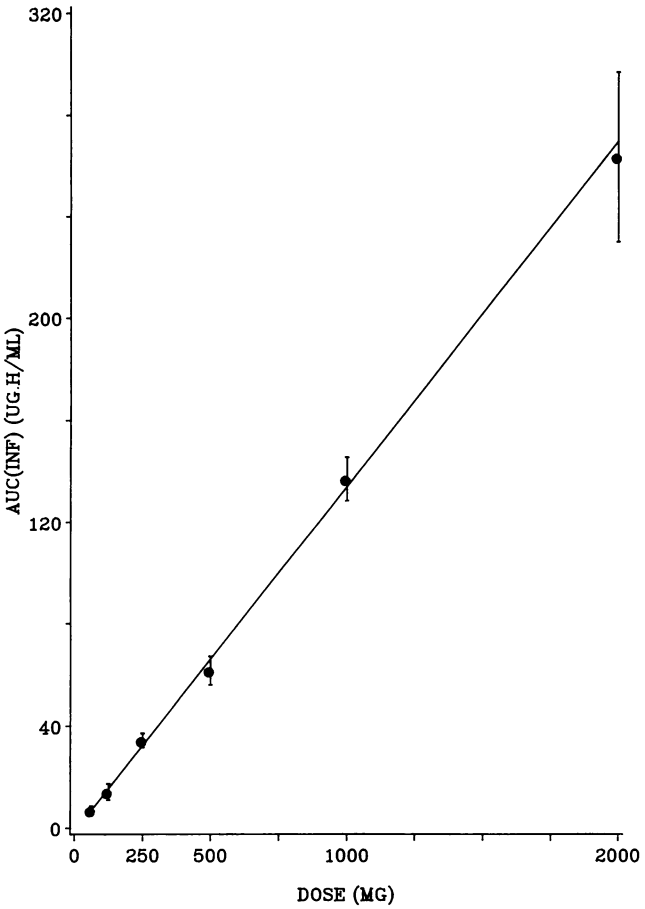

FIG. 4. Linear regression evaluation of $AUC_{0-\infty}$ [AUC(INF)] and cefepime dose ($r = 0.99$; $AUC_{0-\infty} = -1.49 + 0.14 \cdot$ dose).

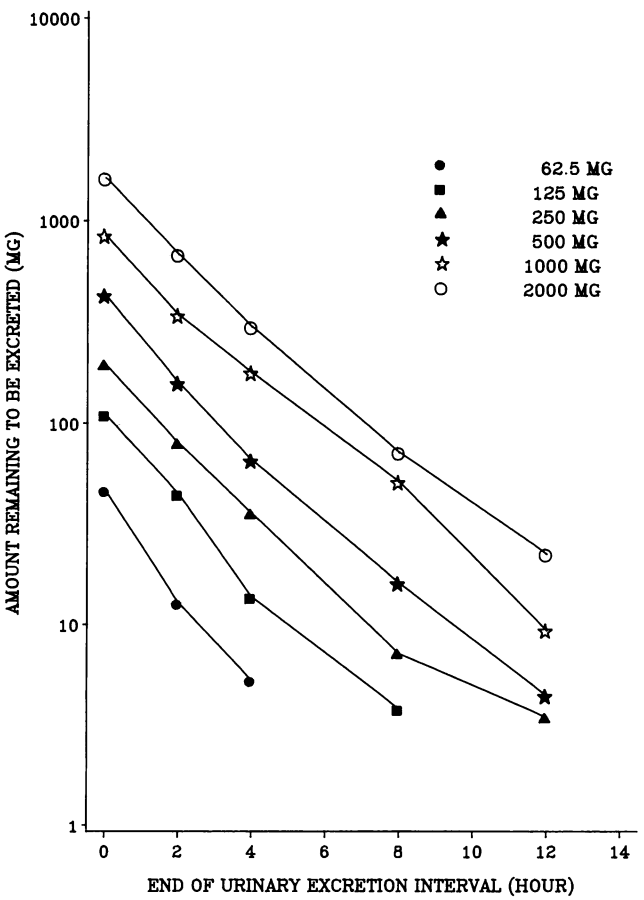

FIG. 5. Evaluation of urinary excretion data for estimation of cefepime $t_{1/2}$.

increased in a dose-proportional manner (Fig. 4). The $t_{1/2}$ values for the 250- to 2,000-mg-dose groups were around 2 h and were independent of the dose. The CL_T estimates ranged from 122 to 136 ml/min within 250- to 2,000-mg-dose groups, and no dose dependency was observed.

Cefepime was primarily excreted by the kidneys. Mean X_u data indicated similar recoveries (percentage of dose) of the intact cephalosporin at all six dose levels (Table 1). Since most of the dose was recovered unchanged in the urine, it appears that cefepime is not significantly metabolized in the body and that the primary clearance mechanism of this cephalosporin is renal excretion. The mean (±SD) CL_R of 105 (±15) ml/min is nearly the same as that of creatinine clearance in normal humans.

The amount of intact cefepime remaining to be excreted (ARE) at the end of each collection interval was calculated for each individual subject. Mean values derived from this evaluation (Fig. 5) are clearly indicative of dose-independent elimination. Individual subject data for the two lowest dose groups were too limited for further evaluation. For individuals who received 250- to 2,000-mg doses, the regression of ln(ARE) on time was evaluated to estimate the $t_{1/2}$. The $t_{1/2}$ values based on urine excretion kinetics were generally consistent with those based on the rate of decline in plasma cefepime concentration (Table 1). Mean (SD) $t_{1/2}$ values from the urine evaluation were 2.4 (0.8), 2.0 (0.7), 2.0 (0.2), and 2.1 (0.3) h for doses of 250, 500, 1,000, and 2,000 mg, respectively.

DISCUSSION

Pharmacokinetic studies with monkeys indicated that cefepime exhibits linear pharmacokinetics and that glomerular filtration is the major route of elimination of this cephalosporin (7). The results of the present study indicate that the concentrations of cefepime in plasma increased with increasing dose in a dose-proportional manner and dose-independent parameters such as mean residence time, CL_T, and CL_R remained independent of dose. The $t_{1/2}$ of cefepime was approximately 2 h and did not appear to vary over the 250- to 2,000-mg-dose range. The $t_{1/2}$ value of cefepime is very similar to those for ceftazidime (3, 8, 15) and cefpirome (1, 10).

Cefepime was eliminated from the body primarily via the kidneys. Approximately 82% of the administered dose was recovered as unchanged cefepime in urine. This is in marked contrast to cefoperazone (5), cefotaxime (5), ceftriaxone (13), and ceftizoxime (11), of which only 25, 55, 60, and 70% of the administered dose is recovered intact in the urine, respectively. The $\%X_u$ for cefepime is very similar to those reported for ceftazidime (3, 8, 15) and cefpirome (1, 10). Mean CL_R estimates for cefepime are about 105 ml/min, a value very similar to that of creatinine clearance in young healthy humans. It seems likely that the CL_R of cefepime, like that of ceftazidime (3, 8, 15), occurs by glomerular filtration, with negligible tubular secretion.

Cefepime offers one of the broadest in vitro spectra of antimicrobial activity of the broad-spectrum cephalosporins

(4, 9, 18). The pharmacodynamic activities of this class of drugs seem to be determined by the duration of time over which concentrations in plasma remain above the MICs for susceptible organisms (6, 12). Cefepime levels have been shown to remain above 1 μg/ml, an effective in vitro MIC for 50% of strains of many gram-positive and gram-negative microorganisms, for at least 8 h after intravenous doses of 500 to 2,000 mg. Cefepime is very poorly bound (16%) to serum proteins (2). These data indicate that the circulating levels of cefepime are primarily in the microbiologically active, free form. The urinary concentrations of cefepime were several times higher than the MIC for 90% of strains of most susceptible urinary tract pathogens for at least 8 to 12 h after single 250- to 2,000-mg intravenous doses. Therefore, in spite of the fact that the cefepime $t_{1/2}$ is about 2 h, the presence of microbiologically active concentrations in plasma and urine for up to 8 to 12 h after drug administration suggests that a twice-daily (every-12-h) dosage schedule of cefepime would be adequate to treat most infections caused by susceptible bacteria.

The pharmacokinetic properties of cefepime, when combined with the broad spectrum of activity and high potency across this spectrum, make cefepime an important addition to the existing armamentarium of anti-infective agents. It is well tolerated after intravenous administration, and its pharmacokinetics appear to be linear within the 250- to 2,000-mg-dose range.

LITERATURE CITED

1. **Badian, M., J. D. Malerczyk, G. T. Collins, M. Dixon, M. Verho, and H. G. Eckert.** 1988. Safety, tolerance and pharmacokinetics of 2.0 g cefpirome (HR810) after single and multiple dosing. Chemotherapy (Basel) **34**:367–373.
2. **Barbhaiya, R. H., S. T. Forgue, W. C. Shyu, E. A. Papp, and K. A. Pittman.** 1987. High-pressure liquid chromatographic analysis of BMY-28142 in plasma and urine. Antimicrob. Agents Chemother. **31**:55–59.
3. **Bergen, T.** 1984. Pharmacokinetics of β-lactam antibiotics. Scand. J. Infect. Dis. Suppl. **42**:83–98.
4. **Clarke, A. M., S. J. V. Zemcov, and J. M. Wright.** 1985. HR-810 and BMY-28142, two new cephalosporins with broad-spectrum activity: an *in-vitro* comparison with other beta-lactam antibiotics. J. Antimicrob. Chemother. **15**:305–310.
5. **Coombes, J. D.** 1982. Metabolism and pharmacokinetics of the newer cephalosporins: cefotaxime, ceftizoxime, ceftriaxone, ceftazidime, cefoperazone, moxalactam and cefsulodin, p. 177–214. *In* H. C. Neu (ed.), New beta-lactam antibiotics: a review from chemistry to clinical efficacy of the new cephalosporins. Proceedings of the Cephalosporins Symposium of the American College of Clinical Pharmacology. Francis Clark Wood Institute for History of Medicine, College of Physicians of Philadelphia, Philadelphia.
6. **Drusano, G. L.** 1988. Role of pharmacokinetics in the outcome of infections. Antimicrob. Agents Chemother. **32**:289–297.
7. **Forgue, S. T., W. C. Shyu, C. R. Gleason, K. A. Pittman, and R. H. Barbhaiya.** 1987. Pharmacokinetics of the novel cephalosporin cefepime (BMY-28142) in rats and monkeys. Antimicrob. Agents Chemother. **31**:799–804.
8. **Kemmerich, B., H. Warns, H. Lode, K. Borner, P. Koeppe, and H. Knothe.** 1983. Multiple-dose pharmacokinetics of ceftazidime and its influence on fecal flora. Antimicrob. Agents Chemother. **24**:333–338.
9. **Kessler, R. E., M. Bies, R. E. Buck, D. R. Chisholm, T. Pursiano, Y. H. Tsai, M. Misiek, K. E. Price, and F. Leitner.** 1985. Comparison of a new cephalosporin, BMY 28142, with other broad-spectrum β-lactam antibiotics. Antimicrob. Agents Chemother. **27**:207–216.
10. **Maab, L., V. Malerczyk, and M. Verho.** 1988. Pharmacokinetics of cefpirome (HR810), a new cephalosporin derivative administered intramuscularly and intravenously to healthy volunteers. Infection **15**:207–210.
11. **Neu, H. C., and S. Subramaniam.** 1981. Pharmacology of ceftizoxime compared with that of cefamandole. Antimicrob. Agents Chemother. **20**:366–369.
12. **Odenholt-Tornquist, I.** 1989. Pharmacodynamics of beta-lactam antibiotics. Studies on the paradoxical and postantibiotic effects *in vitro* and in an animal model. Scand. J. Infect. Dis. Suppl. **58**:1–55.
13. **Patel, I. H., S. Chen, M. Parsonnet, M. R. Hackman, M. A. Brooks, J. Konikoff, and S. A. Kaplan.** 1981. Pharmacokinetics of ceftriaxone in humans. Antimicrob. Agents Chemother. **20**:634–641.
14. **Phelps, D. J., D. D. Carlton, C. A. Farrell, and R. E. Kessler.** 1986. Affinity of cephalosporins for β-lactamases as a factor in antibacterial efficacy. Antimicrob. Agents Chemother. **29**:845–848.
15. **Richards, D. M., and R. N. Brogden.** 1980. Ceftazidime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs **29**:105–161.
16. **Ritschel, W. A.** 1982. Handbook of basic pharmacokinetics, 2nd ed., p. 284–295. Drug Intelligence Publications, Hamilton, Ill.
17. **Täuber, M. G., C. J. Hackbarth, K. G. Scott, M. G. Rusnak, and M. A. Sande.** 1985. New cephalosporins cefotaxime, cefpimizole, BMY 28142, and HR 810 in experimental pneumococcal meningitis in rabbits. Antimicrob. Agents Chemother. **27**:340–342.
18. **Tsuji, A., A. Maniatis, M. A. Bertram, and L. S. Young.** 1985. In vitro activity of BMY-28142 in comparison with those of other β-lactam antimicrobial agents. Antimicrob. Agents Chemother. **27**:515–519.