ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1987, p. 799–804
0066-4804/87/050800-06$02.00/0

Vol. 31, No. 5

Pharmacokinetics of the Novel Cephalosporin Cefepime (BMY-28142) in Rats and Monkeys

S. THOMAS FORGUE,[1]* WEN CHYI SHYU,[1] CAROL R. GLEASON,[2] KENNETH A. PITTMAN,[1] AND RASHMI H. BARBHAIYA[1]

Metabolism and Pharmacokinetics Department[1] and Biostatistics/Data Management Department,[2] Pharmaceutical Research and Development Division, Bristol-Myers Company, Syracuse, New York 13221-4755

Received 27 October 1986/Accepted 24 February 1987

The disposition of the novel cephalosporin cefepime (BMY-28142) was characterized for intravenous administration of single doses to rats and cynomolgus monkeys, the species used most extensively for safety evaluation of the compound. Serial blood samples were collected from individual animals, and plasma was analyzed for intact cefepime by a high-pressure liquid chromatography-UV method. Assay results were evaluated by compartmental and noncompartmental methods to characterize pharmacokinetics for each species and dosage regimen. For intravenous (i.v.) bolus administration of 28 to 386 mg/kg (body weight) to rats, total body clearance (CL; 11.0 ml/min per kg) was essentially invariant with the dose; however, the terminal half-life ($t_{1/2}$) and the steady-state distribution volume (V_{ss}) increased with increasing dose level. After administration of 87 to 1,502 mg/kg by i.v. infusion, CL (12.5 ml/min per kg) was again similar for all dose groups. Mean $t_{1/2}$ values (1.3 to 4.6 h) appeared unusually long for a cephalosporin in rats, and inordinately variable. No consistent differences among dose group mean V_{ss} values were found. The maximal concentration of drug in plasma at the end of infusion was not a linear function of dose. For the cynomolgus monkey, kinetic parameters for 5-min i.v. infusions were linearly related to dose over the range of 10 to 600 mg/kg. Mean parameter values were $t_{1/2}$ = 1.7 h, CL = 1.6 ml/min per kg, and V_{ss} = 0.21 liters/kg. The pharmacokinetic results indicate substantive differences between the two species with respect to their response to toxicologic doses of cefepime.

Cefepime (BMY-28142) is a novel, semisynthetic cephalosporin that is under development for parenteral human therapy. It differs from other aminothiazolyl methoxyimino derivatives like cefotaxime and ceftizoxime by having a quaternized *N*-methyl pyrrolidino moiety attached to the methylene group at C-3 (Fig. 1). The compound has excellent activity against a broad spectrum of clinically important pathogens, including *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains resistant to other new, broad-spectrum cephalosporins (6, 9, 24).

Extensive preclinical safety evaluations have been conducted with cynomolgus monkeys and rats, the latter being appreciably more susceptible to toxicity at high cefepime doses. The present study was conducted to characterize cefepime disposition in these species after single-dose administration. Dose levels and other administration parameters were selected to mimic those of the toxicologic studies.

MATERIALS AND METHODS

Antibiotic formulations. Cefepime was provided by the Pharmaceutical Product Development Department, Bristol-Myers, Co., Syracuse, N.Y., as the sulfate salt or the lyophilized dipolar ion (M_r, 481).

The initial formulation, used for rat bolus doses of 28 and 89 mg/kg (body weight), entailed the combination of cefepime sulfate with $NaHCO_3$ and L-lysine in a 10:1:2.9 weight ratio and dissolution in sterile water for injection. Subsequently, lyophilized dipolar ions were reconstituted with sterile water to yield 250- or 500-mg/ml solutions. These were subsequently diluted with sterile water to prepare solutions used for dosing. Each formulation was prepared on the day of dosing; a portion was stored (−20°C) pending analysis for cefepime content by a high-pressure liquid chromatography-UV assay.

Rat i.v. bolus study. Male Sprague-Dawley rats [Crl:COBS(SD)BR; Charles River Breeding Laboratories, Inc., Wilmington, Mass.] were housed individually with ad libitum access to food and rodent chow, which was withdrawn about 2 h before dosing. The rats weighed 255 to 400 g at dosing. On the day before dosing, a catheter was implanted in the right external jugular vein of each rat, under anesthesia. The catheterization procedure was essentially that described by others (2). The catheter was kept patent with heparinized saline (10 U/ml) overnight and with normal saline during the sampling interval. Each dose of 28, 89, 200, or 386 mg/kg was administered as a bolus (ca. 20-s) injection into a caudal vein. Blood (0.25 ml) was collected into a syringe, previously flushed with heparinized saline, at the following times: 3, 9, 15, and 30 min and 1, 2, 3, 4, and 5 h postdose.

Rat infusion study. Male rats, weighing 290 to 400 g, were catheterized 1 to 2 days before dosing. Each rat received a single dose of 87, 371, 891, 1,440, or 1,502 mg of cefepime per kg infused for 15 min into a caudal vein at a constant rate with a Harvard model 944 pump. Two additional groups of rats received either 807 mg/kg over 5 min or 864 mg/kg over a 10-min infusion period. The dose volume was 1.5 ml/kg for every rat. A plastic restraint device (Harvard Apparatus, South Natick, Mass.) was used during infusion. Heparinized blood samples were collected at the following times after the termination of infusion: 1, 3, 6, 15, and 30 min and 1, 2, 3.5, 5, 6.5, and 8 h. For the lowest (87-mg/kg)-dose group, the last five sampling times were 1.5, 2, 2.5, 3, and 3.5 h. The blood depletion volume was estimated as 15% total blood volume of a 300-g rat.

* Corresponding author.

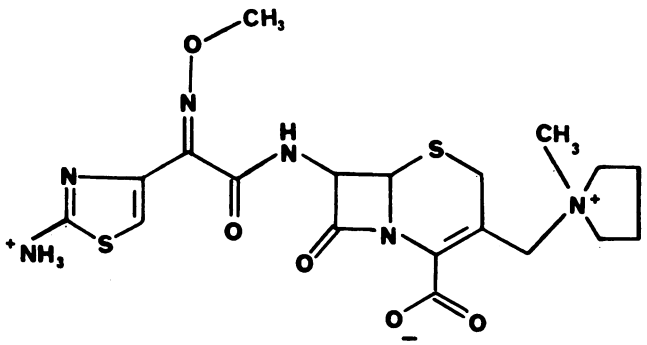

FIG. 1. Structure of the cephalosporin cefepime, 7-[α-(2-aminothiazol-4-yl)-α-(Z)-methoximinoacetamido]-3-[(1-methyl-1-pyrrolidinio)-methyl]-3-cephem-4-carboxylate.

Monkey infusion study. Three male cynomolgus monkeys, weighing 4.0 to 6.3 kg, each received single doses of 10, 100, 300, and 600 mg of cefepime per kg according to a crossover design. A recovery period of at least 2 weeks followed each dosing session. The saphenous vein of each leg was catheterized with an i.v. placement unit (20-gauge by 2.5 cm; A-Cath Teflon; Delmed, Inc., Canton, Mass.) that was kept patent with sterile normal saline; one catheter was used for dosing, and the other was used for sampling. All doses were administered as 5-min, constant-rate infusions (0.48 ml/min per kg) into a saphenous vein by means of the Harvard pump. During drug administration and the first 1 to 2 h of collection, the monkeys were held on a restraint board. Thereafter, blood samples were obtained by venipuncture of the femoral vein during brief manual restraint. Sampling times relative to the start of the 5-min infusions were 6, 9, 15, and 30 min and 1, 2, 3, 4, 6, 8, and 10 h. The blood depletion volume was estimated as 12% total blood volume of the smallest monkey.

Plasma assays. Plasma was prepared from blood by centrifugation and was analyzed for intact cefepime by a validated high-pressure liquid chromatography-UV method (3). The accuracy and precision of the analyses were verified with control samples that were stored and assayed with the study samples.

Pharmacokinetic analyses. Plasma cefepime concentration-versus-time data were evaluated by both compartmental and noncompartmental pharmacokinetic methods. A noncompartmental value for the elimination half-life ($t_{1/2}$) was calculated as (ln 0.5)/b, where b was the slope of the least-squares regression line for n terminal datum points, with n selected to maximize the correlation coefficient. The maximal concentration of drug in plasma (C_{max}) observed at the termination of infusion was taken as the noncompartmental C_{max} value. The area under the concentration versus time curve (AUC) and the area under the first moment of the curve (AUMC) were estimated by the trapezoidal method and by the log-trapezoidal method during the terminal, log-linear phase. The terms C'/b and (C'/b) $(t' + 1/b)$ were used for AUC and AUMC calculations, respectively, for extrapolation to infinite time, where C' was the concentration predicted from the terminal regression line for t', the last sampling time (13). Mean residence time in the body (MRT) was estimated as MRT = (AUMC/AUC) − $T/2$, where T was the infusion duration; T = 0 for bolus dosing. Total body clearance (CL; CL = dose/AUC) and steady-state distribution volume [V_{ss}; V_{ss} = MRT(CL)] were also calculated.

Initial estimates of compartmental parameters were obtained by the method of residuals (7). Subsequently, the concentration-versus-time data were fit to bi- or triexponential functions representative of two- or three-compartment open models (central-compartment elimination), by means of the iterative, least-squares, nonlinear regression programs of NONLIN84 (16). A weight of $1/C^2$ was usually applied to the individual subject datum sets. The "goodness of fit" was evaluated on the basis of the diagnostic statistics calculated by NONLIN84 subroutines for each estimation job and by subjective comparison of predicted and actual concentration-versus-time plots. Optimized "macro" constants for infusion administration were converted to their bolus i.v. equivalents, as described by Loo and Riegelman (13). The coefficients and exponents for the characteristic bolus function were then used to derive the following parameters by standard equations: C_{max}, AUC, AUMC, $t_{1/2}$, MRT, CL, and V_{ss} (4, 7, 13, 19, 25).

Statistical methods. The significance of differences between mean pharmacokinetic parameters was evaluated either by a one-way analysis of variance (ANOVA) model (rat studies) or by a randomized-blocks ANOVA model (monkey study) (10). Dose-dependent parameters were evaluated after normalization for dose level. The Tukey or Tukey-Kramer multiple comparison procedure was used to compare mean values at each dose level for which significant differences were found. The upper bound on the type I error was held at $\alpha = 0.05$. In cases in which substantial heterogeneity of variance among groups was observed, a rank transformation was applied to the data, and comparisons were made on the basis of the ranks (5).

Regression analyses (18) were also used to evaluate dose-dependent parameters. Adequacy of a linear fit of the parameter-versus-dose relation was evaluated by computing a lack of fit statistic based on a partitioning of the pure error from the residual error. In cases of nonhomogeneous variance, weighted linear regression was used, where the weights were the reciprocals of the variances at each dose level. Significance of slope, intercept, and goodness-of-fit estimates were assessed at the 5% level.

RESULTS

Bolus administration to rats. A primary objective of the initial rat study was to determine whether kinetic parameters varied linearly with bolus dose. Serial blood samples were collected from each individual rat after administration of a single i.v. dose of cefepime. Concentrations of the intact cephalosporin in plasma were determined as a function of

TABLE 1. Pharmacokinetic parameters for bolus i.v. administration of cefepime to rats[a]

Bolus dose (mg/kg)	Pharmacokinetic parameter estimates[b] (SD)				
	$t_{1/2}$ (h)	MRT (h)	AUC[c] (μg · h/ml)	CL (ml/min per kg)	V_{ss} (liters/kg)
28	0.39 (0.02)	0.51 (0.03)	1.58 (0.28)	10.8 (2.2)	0.33 (0.05)
89	0.65 (0.18)	0.59 (0.11)	1.54 (0.24)	11.0 (1.7)	0.38 (0.04)
200	2.0 (1.9)	0.74 (0.42)	1.53 (0.44)	11.7 (3.3)	0.46 (0.14)
386	2.3 (1.8)	0.92 (0.52)	1.63 (0.25)	10.4 (1.4)	0.56 (0.31)

[a] Data are dose group mean values from compartmental analyses for five to seven individuals.

[b] Statistics based on ANOVA. Rank transformations applied to all parameters except AUC and CL. The mean $t_{1/2}$ for the 28-mg/kg dose was significantly less than the means for the 200- and 386-mg/kg doses. The mean $t_{1/2}$ for the 89-mg/kg dose was significantly different from that for the 200-mg/kg dose. No other significant differences were found for any parameter.

[c] Normalized to a 1-mg/kg dose.

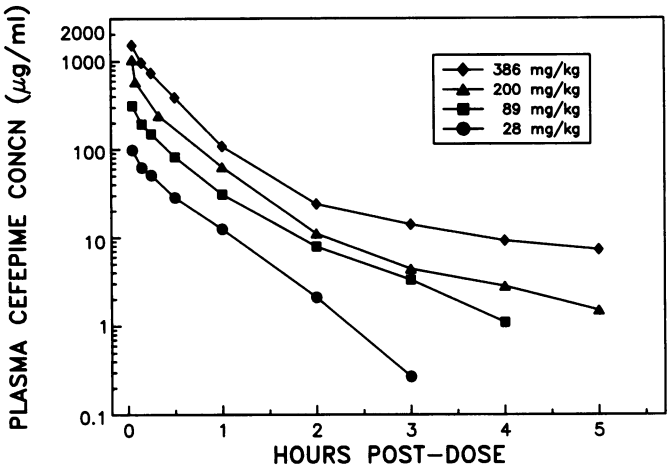

FIG. 2. Plasma cefepime concentrations for bolus i.v. dosing of rats. Serial plasma samples were collected from each individual after a single injection. Each point represents the mean for five to seven rats.

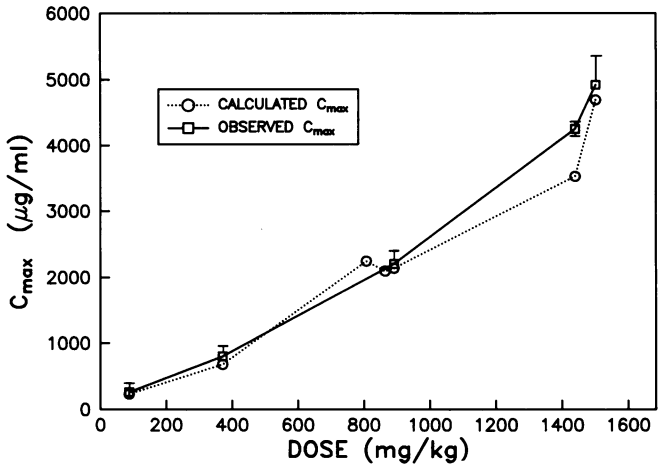

FIG. 3. Relationship between C_{max} and cefepime infusion dose administered to rats. Each calculated C_{max} value is the mean of the compartmental (fitted) values for four or five individuals. Calculated values for 5-min (807 mg/kg) and 10-min (864 mg/kg) infusion intervals were normalized to an infusion time of 15 min for comparison with the other five dose group means. The mean and standard deviation of the plasma drug concentrations actually observed at the end of the 15-min infusions are also shown.

time (Fig. 2). Compartmental pharmacokinetic analyses of the high-pressure liquid chromatography assay data yielded parameter values (Table 1) that were generally equivalent to results obtained by noncompartmental methods.

No significant deviation from a linear relationship between AUC and dose was revealed by regression analysis, and mean CL = 11.0 ml/min per kg was essentially invariant with respect to dose level. There was, however, a consistent increase in V_{ss} over the 14-fold dose range. At the lowest dose level, the mean $t_{1/2}$ value was comparable to that reported for many cephalosporins and was nearly equivalent to MRT(ln 2), as expected (7, 19). This was not the case for doses of 89 mg/kg and above. The intersubject variability of both $t_{1/2}$ and MRT was marked at the higher dose levels. Because of the heterogeneity of variance for these parameters, significant differences among dose groups were not discernable by the ANOVA procedures. On the basis of rank analyses, the significance of group differences in $t_{1/2}$ (Table 1) was apparent.

Infusion administration to rats. The results of acute toxicologic studies indicate that rats tolerate higher doses when cefepime is administered by constant rate infusion rather than as a bolus (T. J. Davidson, Bristol-Myers Co., unpublished results). Pharmacokinetics were characterized for i.v. infusions of 87 to 1,502 mg/kg, administered at a constant rate over a 15-min interval. In addition, doses of approximately 850 mg/kg were infused over 5-, 10-, or 15-min intervals to investigate the effect of infusion interval on disposition. Serial plasma samples were obtained during the postinfusion phase, and the cefepime concentration data for each individual rat were evaluated. Although most datum sets were adequately described by biexponential functions, a triexponential function was most appropriate in a few cases.

Kinetic parameter values (Table 2) derived from the characteristic functions were generally equivalent to the results of noncompartmental evaluation. Mean AUC values appeared essentially invariant with respect to infusion time, linearly related to dose, and consistent with mean values for bolus dosing. No significant differences in CL among the various dose groups were observed, exclusive of the anomalous, 371-mg/kg dose group. An overall mean CL of 12.5 ml/min per kg was obtained. In contrast to the bolus i.v. case, no consistent relationship between V_{ss} and dose was apparent.

TABLE 2. Pharmacokinetic parameters for i.v. infusion administration of cefepime to rats[a]

Dose (mg/kg)	Infusion time (min)	Pharmacokinetic parameter estimates[b] (SD)					
		C_{max} (μg/ml)	$t_{1/2}$ (h)	MRT (h)	AUC[c] (μg · h/ml)	CL (ml/min per kg)	V_{ss} (liters/kg)
87	15	233 (16)	1.3 (0.6)	0.40* (0.05)	1.55* (0.11)	10.8* (0.7)	0.26* (0.04)
371	15	679 (32)	2.4 (0.7)	1.14† (0.47)	1.17† (0.06)	14.3† (0.8)	0.98† (0.40)
807	5	2,903 (1,333)	2.8 (2.8)	0.49 (0.09)	1.43 (0.40)	12.3 (2.9)	0.37 (0.13)
864	10	2,379 (637)	4.6 (4.6)	0.49 (0.16)	1.28 (0.20)	13.1 (1.4)	0.38 (0.12)
891	15	2,136 (377)	1.2 (0.2)	0.53 (0.10)	1.33 (0.20)	12.8 (1.9)	0.40 (0.07)
1,440	15	3,526 (474)	1.8 (0.6)	0.46 (0.11)	1.25 (0.12)	13.4 (1.3)	0.38 (0.08)
1,502	15	4,689 (1,643)	—[d]	—[e]	1.54* (0.24)	11.0* (0.2)	—[f]

[a] Data are dose group mean values from compartmental analyses for four or five individuals.
[b] Statistics based on ANOVA. Rank transformations applied to all parameters except AUC and CL. In each column, means with different symbols are significantly different from one another but not from means without symbols.
[c] Normalized to a 1-mg/kg dose.
[d] No representative mean. Range of values is 1.4 to 16.9 h.
[e] No representative mean. Range of values is 0.3 to 5.6 h.
[f] Indeterminate.

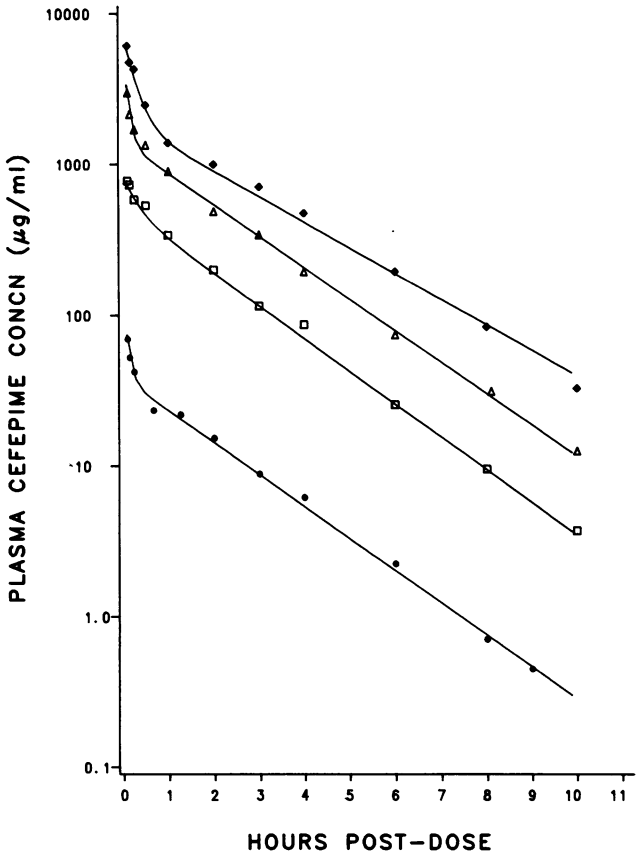

FIG. 4. Plasma cefepime concentrations for a representative cynomolgus monkey. Each dose of 10 (●), 100 (□), 300 (△), or 600 (◆) mg/kg was administered as a 5-min i.v. infusion. A biexponential function optimized by nonlinear regression is represented by a continuous curve for each dose level.

Characterization of $t_{1/2}$ and MRT was less straightforward. The blood collection interval was limited (especially for the 87-mg/kg group) and an unambiguous characterization of the inordinately slow elimination phase for many rats was not possible. All $t_{1/2}$ values were taken as estimates for the purpose of comparisons among the various dose groups. Marked intersubject variability of $t_{1/2}$ values was observed for all groups. Although there were large differences among dose group mean values, large variances precluded statistical verification of these differences. Mean $t_{1/2}$ values were consistently greater than those of MRT.

C_{max} values, calculated from fitted exponential functions, were reasonably close to actual values observed at the end of infusion. The C_{max} values for 5-, 10-, and 15-min infusions of approximately 850 mg/kg were normalized for infusion duration (and dose) and were compared. No significant differences among these three groups were found. A significant deviation from a linear relationship was apparent for the regression of C_{max} on dose over the 17-fold dose range represented by all seven treatment groups (Fig. 3).

Infusion administration to monkeys. Pharmacokinetics were evaluated for administration of 10 to 600 mg of cefepime per kg to cynomolgus monkeys as 5-min i.v. infusions. Postinfusion drug concentrations in plasma were well characterized by biexponential functions in every case (Fig. 4). Noncompartmental evaluations yielded values equivalent to compartmental results (Table 3). All parameters, including C_{max} (Fig. 5), were linearly related to dose. Overall mean values were $t_{1/2}$ = 1.7 , MRT = 2.2 h, CL = 1.6 ml/min per kg, and V_{ss} = 0.21 liters/kg. These results were close to those expected for a dipolar ionic cephalosporin, e.g., V_{ss} approximated extracellular fluid volume. Intersubject variability was low and similar for all dose groups.

DISCUSSION

The pharmacokinetics of the novel cephalosporin cefepime have been described for the two major toxicologic species, rats and monkeys, used for acute and subchronic safety testing. The study results indicate substantive differences between the two species with respect to their response to toxicologic doses of cefepime.

A definitive evaluation of cefepime kinetics in rats has not been achieved for any given dosage regimen. For example, the accuracy of $t_{1/2}$ values for some rats is questionable. It is technically difficult to characterize the concentration of drug in serum as a function of time during the transient distribution phase, define a $t_{1/2}$ of several hours, and minimize trauma by restricting the number of blood samples taken, especially from high-dose animals, which may be physiologically impaired.

Despite these limitations, it is clear that in rats, cefepime displays nonlinear kinetics that cannot be ascribed to changes in CL. The most remarkable finding is related to the terminal elimination phase. At the lowest (28-mg/kg) dose level, $t_{1/2}$ is typical of that for many cephalosporins (17, 20). Variability among individual rat values is quite low. At other dose levels, the apparent $t_{1/2}$ is unusually long and variable and exceeds the corresponding MRT estimate. The latter result is evidence that assumptions of linear kinetic behavior, e.g., first-order processes, and elimination exclusively from the central compartment, upon which these MRT calculations are based (4, 8, 19), may not be applicable. The lack of dose proportionality in C_{max} is additional evidence for nonlinear processes.

Dispositional parameters for all individual monkeys were similar and clearly indicative of linear kinetics over the

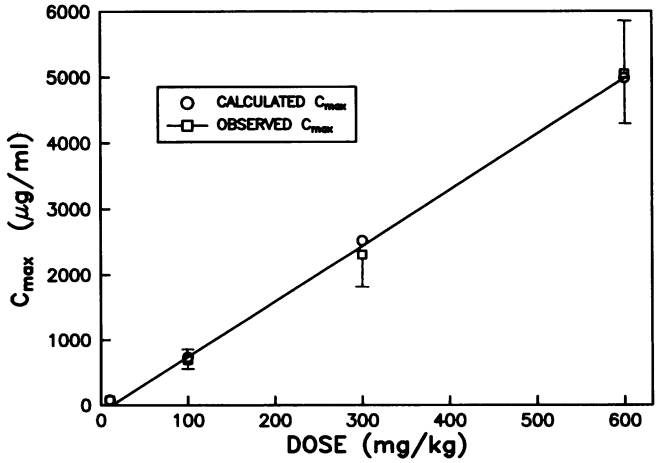

FIG. 5. Relationship between C_{max} and cefepime infusion dose administered to cynomolgus monkeys. Each calculated C_{max} value is the mean of the compartmental (fitted) values for three individuals. A least-squares regression line and the standard deviations of the plasma drug concentrations actually observed at the end of infusion are also shown.

TABLE 3. Pharmacokinetic parameters for i.v. infusion (5-min) administration of cefepime to cynomolgus monkeys[a]

Dose (mg/kg)	Pharmacokinetic parameter estimates[b] (SD)					
	C_{max} (μg/ml)	$t_{1/2}$ (h)	MRT (h)	AUC[c] (μg · h/ml)	CL (ml/min per kg)	V_{ss} (liters/kg)
10	80 (17)	1.8 (0.3)	2.3 (0.5)	9.3 (1.1)	1.8 (0.2)	0.25 (0.02)
100	740 (19)	1.5 (0.1)	2.1 (0.2)	10.4 (1.3)	1.6 (0.2)	0.20 (0.04)
300	2,520 (660)	1.7 (0.4)	2.3 (0.6)	11.1 (1.3)	1.5 (0.2)	0.20 (0.03)
600	4,980 (840)	1.8 (0.2)	2.2 (0.3)	10.5 (2.6)	1.7 (0.4)	0.20 (0.03)

[a] Data are dose group mean values from compartmental analyses for three individuals.
[b] Statistics were determined from dose group comparisons and were not determined for C_{max}. For the other parameters, there is no statistically significant difference.
[c] Normalized to a 1-mg/kg dose.

60-fold dose range. The overall mean $t_{1/2}$, 1.7 h, is greater than that reported for most other cephalosporins in Macaca species. Estimates based on recent literature are the following: cefmetazole, 0.5 h (17, 21); cefamandole, 0.6 h (17); cefazolin, 0.7 h (12, 22); ceftizoxime, 0.7 h (17); cefotaxime, 0.8 h (17); ceftazidime, 0.8 h (1); HR 810, 1.2 h (11); cefotetan, 1.3 h (12, 22); cefpiramide, 2.5 h (15); and ceftriaxone, 3.4 h (14). The slow elimination of the latter two compounds may reflect their being highly sequestered by plasma proteins. In contrast, cefepime has negligible binding in all species tested (3, 9). Low binding, and the fact that CL values are roughly half of inulin clearance values, viz., 3.1 ml/min per kg, for this primate (23), indicate that cefepime may be subject to appreciable tubular reabsorption. The V_{ss} results do not reveal any remarkable difference from other β-lactam agents, which tend to distribute to total extracellular water.

Rats are the most sensitive of the species challenged acutely with toxicologic doses of cefepime. This idiopathic sensitivity renders pharmacokinetic evaluations of special interest as a potential reflection of physiologic alterations. Recently, rats have been identified as having a unique predisposition for cardiovascular effects after acute challenge with certain cephalosporins, such as cefepime and cephaloridine (T. J. Davidson, Bristol-Myers Co., personal communication). The atypical dispositional characteristics of rats could be sequelae of transient hemodynamic disturbances that are in turn complex functions of dose and administration rate.

ACKNOWLEDGMENTS

We thank Jeannine Briedis, David Henry, Prasad Kari, Eugene Papp, and Vinod Shah for their excellent technical support.

LITERATURE CITED

1. **Acred, P.** 1983. Therapeutic and kinetic properties of ceftazidime in animals. Infection **11**(Suppl. 1):544–548.
2. **Bakar, S. K., and S. Niazi.** 1983. Simple reliable method for chronic cannulation of the jugular vein for pharmacokinetic studies in rats. J. Pharm. Sci. **72**:1027–1029.
3. **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.
4. **Benet, L. Z., and R. L. Galeazzi.** 1979. Noncompartmental determination of the steady-state volume of distribution. J. Pharm. Sci. **68**:1071–1074.
5. **Conover, W. J., and R. L. Iman.** 1981. Rank transformations as a bridge between parametric and nonparametric statistics. Am. Stat. **35**:124–133.
6. **Conrad, D. A., R. K. Scribner, A. H. Weber, and M. I. Marks.** 1985. In vitro activity of BMY-28142 against pediatric pathogens, including isolates from cystic fibrosis sputum. Antimicrob. Agents Chemother. **28**:58–63.
7. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, 2nd ed., p. 63–74, 409–417, and 433–444. Marcel Dekker, Inc., New York.
8. **Gillespie, W. R., and P. Veng-Pedersen.** 1985. The determination of mean residence time using statistical moments: is it correct? J. Pharmacokinet. Biopharm. **13**:549–554.
9. **Kessler, R. E., M. Bies, R. E. Buck, D. R. Chisholm, T. A. 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. **Kirk, R. E.** 1968. Experimental design: procedures for the behavioral sciences, p. 131–145. Wadsworth Co., Belmont, Calif.
11. **Klesel, N., and K. Seeger.** 1983. Pharmacokinetic properties of the new cephalosporin antibiotic HR 810 in animals. Infection **11**:318–321.
12. **Komiya, M., Y. Kikuchi, A. Tachibana, and K. Yano.** 1981. Pharmacokinetics of a new broad-spectrum cephamycin, YM09330, parenterally administered to various experimental animals. Antimicrob. Agents Chemother. **20**:176–183.
13. **Loo, J. C. K., and S. Riegelman.** 1970. Assessment of pharmacokinetic constants from postinfusion blood curves obtained after I.V. infusion. J. Pharm. Sci. **59**:53–55.
14. **Matsui, H., M. Komiya, C. Ikeda, and A. Tachibana.** 1984. Comparative pharmacokinetics of YM-13115, ceftriaxone, and ceftazidime in rats, dogs, and rhesus monkeys. Antimicrob. Agents Chemother. **26**:204–207.
15. **Matsui, H., K. Yano, and T. Okuda.** 1982. Pharmacokinetics of the cephalosporin SM-1652 in mice, rats, rabbits, dogs, and rhesus monkeys. Antimicrob. Agents Chemother. **22**:213–217.
16. **Metzler, C. M., and D. L. Weiner.** 1984. NONLIN84 user's guide. Statistical Consultants, Inc., Lexington, Ky.
17. **Murakawa, T., H. Sakamoto, S. Fukada, S. Nakamoto, T. Hirose, N. Itoh, and M. Nishida.** 1980. Pharmacokinetics of ceftizoxime in animals after parenteral dosing. Antimicrob. Agents Chemother. **17**:157–164.
18. **Neter, J., and W. Wasserman.** 1976. Applied linear statistical models, p. 21–96. R. O. Irwin, Inc., Homewood, Ill.
19. **Riegelman, S., and P. Collier.** 1980. The application of statistical moment theory to the evaluation of *in vitro* dissolution time and absorption time. J. Pharmacokinet. Biopharm. **8**:509–534.
20. **Sawata, Y., M. Hanano, Y. Sugiyama, and T. Iga.** 1984. Prediction of the disposition of β-lactam antibiotics in humans from pharmacokinetic parameters in animals. J. Pharmacokinet. Biopharm. **12**:241–261.
21. **Shindo, H., K. Kawai, T. Ikeda, I. Igarashi, and S. Sugawara.** 1982. Absorption, distribution, excretion and metabolism of cefmetazole in cynomolgus monkeys. J. Antibiot. **35**:742–754.
22. **Suzuki, H., K. Imamura, T. Yoshida, M. Shibata, T. Matsuzawa, H. Ozaki, T. Sakai, Y. Shiobara, A. Tachibana, and K. Yano.** 1983. Animal pharmacokinetics and toxicology of cefotetan—a new cephamycin antibiotic. J. Antimicrob. Chemother. **11**:(Suppl. 11A):179–183.

23. **Sweet, A. Y., M. F. Levitt, and H. L. Hodes.** 1961. Kidney function, body fluid compartments, and water and electrolyte metabolism in the monkey. Am. J. Physiol. **201**:975–979.
24. **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.
25. **Wagner, J. G.** 1976. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J. Pharmacokinet. Biopharm. **4**:443–467.