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Effects of Age and Gender on Pharmacokinetics of Cefepime

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The effects of age and gender on the pharmacokinetics of cefepime were examined in 48 volunteers following administration of a single 1,000-mg intravenous dose. Male and female subjects were divided into four groups, each consisting of 12 subjects, according to their age and gender. The young subjects were between 20 and 40 years of age and elderly subjects were between 65 and 81 years of age. Serial blood and urine samples were collected from each subject and were analyzed for cefepime by validated high-pressure liquid chromatographic assays with UV detection. Key pharmacokinetic parameters were calculated by noncompartmental methods. There were no gender-related differences in elimination half-life ($t_{1/2}$) and weight-normalized total body clearance (CL_T), renal clearance (CL_R), and steady-state volume of distribution (V_{ss}). Statistically significant age-related effects were found for $t_{1/2}$, CL_T, CL_R, and V_{ss} parameters. In different study groups, V_{ss} ranged from 0.21 to 0.24 liter/kg. The values for V_{ss} were significant greater for elderly subjects than they were for young subjects. The cefepime $t_{1/2}$ was significantly longer in elderly subjects (about 3 h) than that observed in young subjects (about 2.2 h). The mean values for CL_T and CL_R in the four study groups ranged from 1.11 to 1.56 and 0.99 to 1.44 ml/min/kg, respectively. In elderly subjects, the estimates for CL_T and CL_R were significantly lower than those observed in young subjects. Linear regression revealed good correlations between clearance values of cefepime and creatinine. The magnitude of age-related changes in the pharmacokinetics of cefepime is not significant enough to recommend dosage adjustment in elderly patients with kidney functions normal for their age.

Cefepime (BMY-28142) is a new parenteral "fourth-generation" cephalosporin antibiotic with a spectrum of antimicrobial activity broader than those of other new cephalosporins and nontraditional antibiotics (12, 18). The in vitro activities of cefepime have been reproduced in numerous in vivo infection models (19, 28). Compared with cefotaxime, cefepime has been shown to be five- to ninefold more active against *Pseudomonas aeruginosa* (18). In addition, cefepime has been found to be approximately fourfold more active than ceftazidime against gram-positive organisms (12, 18). Cefepime was also more active than ceftazidime, moxalactam, cefoperazone, cefpirome, and cefotaxime when the compounds were tested against 326 species of members of the family *Enterobacteriaceae* (18). Cefepime has a low affinity for major chromosomally mediated β-lactamases (24).

Values of key pharmacokinetic parameters after the administration of single and repeated intravenous and intramuscular doses to normal volunteers indicate that cefepime is safe and well-tolerated and exhibits linear pharmacokinetics within the 62.5- to 2,000-mg dose range (2, 3, 7).

In normal subjects, cefepime is cleared primarily by urinary excretion in the unchanged form (2, 3, 6, 7). Previous clinical studies with other cephalosporins indicate that the elimination half-life ($t_{1/2}$) is prolonged in elderly patients (23). Both male and female patients of different age groups are potential recipients of cefepime therapy. The aim of this study was to characterize the safety, tolerance, and pharmacokinetics of a single intravenous dose of cefepime in healthy men and women over a wide age range.

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MATERIALS AND METHODS

Subjects. A total of 48 healthy volunteers participated in the study after providing written informed consent. There were 12 men and 12 women aged 20 to 40 years (groups 1 and 2, respectively) and 12 men and 12 women aged 65 to 81 years (groups 3 and 4, respectively). The weights of all individuals were within 10% of the ideal body weights for their heights. The creatinine clearance (CL_{CR}) values for individual subjects were calculated by dividing the amount of creatinine excreted in urine over a 12-h period by the concentration of creatinine in plasma at 6 h. The observed CL_{CR} values met the minimum values for that subject's age and weight (26). The demographic data are given in Table 1.

Subject ineligibility criteria included compromising drug allergies or intolerance, a history of drug or alcohol abuse, and a positive test result for controlled substance screening conducted the evening preceding dosing. Subjects with a history or evidence of chronic infectious disease, heart disease, pulmonary obstructive disease, bronchial asthma, hypertension, renal or hepatic impairment, gastrointestinal disease, glaucoma, or a positive test for human immunodeficiency virus antibodies or hepatitis B surface antigens were excluded. Women were required to practice a method of birth control (excluding oral contraceptives and the Progestasert intrauterine device), have a negative pregnancy test at the time of screening and on admission to the study, or be surgically sterile or postmenopausal. Use of any medication known to induce or inhibit drug-metabolizing enzymes (e.g., rifampin, cimetidine, or compounds in the barbiturate and phenothiazine classes) within 1 week of the study and the use of alcohol within 48 h of induction into the study was not permitted. Use of any drug, including alcohol and caffeine, during the study was not allowed. The subjects were instructed to refrain from smoking before dosing and for 4 h after drug administration. Confinement to the test

facility began the evening before cefepime administration and continued until the subjects were released from the study. Since the drug was administered intravenously, no fasting was required. To ensure adequate diuresis for urine sampling, subjects drank 400 ml of water 2 h before the infusion and approximately 150 ml of water every hour for 4 h after the infusion. Subjects were required to be ambulatory for at least 10 min every half hour for the first 2 h after dosing and were not permitted to engage in strenuous exercise in the facility during the study period.

Drug formulation and administration. Lyophilized cefepime was supplied by the Pharmaceutical Product Development Department of Bristol-Myers Squibb Co., Syracuse, N.Y. Each vial contained 1,000 mg of cefepime and 2 mol equivalents each of hydrochloride and L-arginine. Each vial was reconstituted with 2.8 ml of sterile water for injection; this resulted in a clear solution containing 250 mg of cefepime dipolar ionic activity per ml. The reconstituted solution was diluted with sufficient sterile normal saline to prepare cefepime infusion solutions of 20 mg/ml. Each subject received a single 1,000-mg dose of cefepime as a constant-rate infusion into a forearm vein by means of a syringe pump calibrated to deliver 50 ml of infusion solution per 30-min interval. Administration was via a forearm vein contralateral to that used for blood sampling.

Safety evaluation. For each subject, a medical history was taken and a physical examination was performed before the start of the study. A brief physical examination was also performed within 24 h of the start of dosing, and the complete physical examination was repeated after completion of the study. A 12-lead electrocardiogram was obtained before the start of the study, before drug administration on day 1, and 1.5 h after the start of the cefepime infusion. Systolic and diastolic blood pressures, pulse rates, respiratory rates, and oral temperatures were obtained 30 min before dosing and at 15 and 30 min and 1.5 h after the start of dosing. Routine laboratory tests were performed before the start of the study, on admission to the study site on day 0, and before breakfast on day 2 for groups 1 and 2 and day 3 for groups 3 and 4. Laboratory tests included serum chemistries, a routine hematology screen, and urinalysis.

Collection of blood and urine samples. Heparinized blood samples (5 ml) were obtained from the arm contralateral to that used for drug administration. Blood samples were obtained according to the following schedule: predose; 10, 20, 30 (end of infusion), 33, 39, and 45 min; and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 h after the start of drug administration for groups 1 and 2. Blood samples were also obtained at 30, 36, and 48 h from subjects in groups 3 and 4. Immediately after collection, each blood sample was gently inverted a few times for complete mixing with the anticoagulant and was then held on ice. Within 30 min of collection, each blood sample was centrifuged for 15 min, at approximately 1,000 × *g* at 0 to 5°C, to separate the plasma. Plasma samples were stored at or below −20°C.

The total urine output of each subject was collected before dosing and at intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h for groups 1 and 2. Urine collection continued for groups 3 and 4 at 24 to 36 and 36 to 48 h after the start of cefepime infusion. A separate urine collection vessel was used for each collection period, and the containers were refrigerated during and after the collection interval. Total urine volume and pH were recorded. A 3-ml portion of urine was transferred to a polypropylene tube containing buffer solution, mixed, and then frozen at or below −20°C.

Analysis of plasma and urine samples. Plasma and urine samples were analyzed for cefepime by a validated high-pressure liquid chromatographic assay with UV detection (4). Quality control samples of plasma and urine, containing known concentrations of cefepime, were prepared before initiation of drug administration and were stored together with the study samples. The results of the plasma and urine quality control samples were within 10% of the nominal values, and the percent coefficient of variation for replicate assays was less than 8.3%. The results are indicative of accurate and precise analyses and of the adequate stability of cefepime in study samples under storage conditions.

Pharmacokinetic analysis. Plasma cefepime concentration versus time were analyzed by noncompartmental methods (14, 25). The highest observed concentration in plasma and the corresponding sampling time constituted C_{max} and T_{max}, respectively. $t_{1/2}$ was calculated as 0.693/β, where β is the absolute 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 for the regression. The area under the plasma concentration-time curve (AUC) was calculated by using a combination of linear and log trapezoidal rules (25). The log trapezoidal rule was used during those phases when concentrations were declining exponentially. The AUC from the concentration of the last measured time (C_{tn}) to infinity ($AUC_{0-\infty}$) was calculated as C_{tn}/β.

The following pharmacokinetic parameters were estimated: $MRT = AUMC_{0-\infty}/AUC_{0-\infty}$, where MRT is the mean residence time, and AUMC is the area under the first moment of the plasma-concentration time curve. Other parameters were calculated as follows: $MRT_{i.v.} = MRT - (T/2)$, $CL_T = dose/AUC_{0-\infty}$, and $V_{ss} = MRT_{i.v.} \cdot CL_T$, where $MRT_{i.v.}$ is the MRT equivalent for bolus intravenous (i.v.) administration, T is the infusion time, CL_T is the total systemic clearance, and V_{ss} is the volume of distribution at steady state (8).

The amount of intact cefepime excreted in urine for each collection interval was calculated as the product of the concentration in the corresponding buffered urine sample and the total volume of urine voided in that interval. The total urinary recovery was calculated as the cumulative amount excreted within the specified interval of a given dose group and was expressed as a percentage of the administered dose. Renal clearance (CL_R) of cefepime was calculated as $CL_R = X_u/AUC_{0-\infty}$, where X_u is the amount of cefepime excreted in urine. The values for CL_T, CL_R, and V_{ss} for each subject were normalized for body weight.

Statistical analysis. The study was a 2-by-2 factorial design, with age and gender as the two factors. Analysis of variance was used to evaluate the pharmacokinetic parameters C_{max}, $t_{1/2}$, $AUC_{0-\infty}$, $MTR_{i.v.}$, CL_T, CL_R, and V_{ss}. Factors in the analysis of variance model were age, gender and the age-gender interaction. In the absence of a significant age-gender interaction, the comparison between age groups was made by pooling across both genders, and the comparison between genders was made by pooling across both age groups. In the presence of a significant interaction, the age comparison was made within each gender and the gender comparison was made within each age group. All comparisons used the mean-square error from the analysis of variance as the estimate of intersubject variability. The value $P = 0.05$ was used as the significance level for all tests.

RESULTS

Safety and tolerance. A total of 48 healthy men and women entered and completed the study. The study was completed without any serious adverse events. Adverse reactions reported by the subjects included headache (two young and four elderly women), lightheadedness (one young man), and nausea (one elderly woman, who also experienced a headache). All adverse events were mild to moderate in intensity and were normally expected adverse events for any β-lactam antibiotic.

Pharmacokinetic analyses. Mean plasma cefepime concentration-versus-time profiles after administration of a 1,000-mg intravenous dose to female (young and elderly) and male (young and elderly) subjects are shown in Fig. 1 and 2, respectively. All urine samples collected from cefepime-treated subjects were analyzed to determine the urinary recovery of intact cefepime. High urinary concentrations of cefepime were achieved in the subjects, since the majority of the drug was excreted unchanged in urine. The mean ± standard deviation urinary recovery of cefepime accounted for 88.2% ± 7.6%, 92.4% ± 5.8%, 81.1% ± 7.6% and 93.0% ± 11.5% of the dose in young female, young male, elderly female, and elderly male dose groups, respectively.

The mean ± standard deviation pharmacokinetic parameters of cefepime in the four study groups are given in Table 1. The values for the cefepime C_{max} at the end of the 30-min infusion were significantly higher in female than in male volunteers. $AUC_{0-\infty}$ was, similarly, significantly higher for female subjects than for male subjects. Statistically significant age-related effects were found for $t_{1/2}$, CL_T, CL_R, and V_{ss}. The mean values for V_{ss} in different study groups ranged from 0.21 to 0.24 liter/kg. There was no significant difference between males and females. However, V_{ss} values for elderly subjects were significantly greater than those for young subjects. Cefepime elimination varied among young and elderly subjects. The $t_{1/2}$ estimates in elderly subjects (about 3 h) were significantly longer than those observed in young subjects (about 2.2 h). There were no differences in $t_{1/2}$ between males and females. The mean values for CL_T and CL_R in young and elderly subjects ranged from 1.11 to 1.54 and 0.99 to 1.44 ml/min/kg, respectively. CL_T and CL_R values for elderly subjects were significantly lower than those for young subjects. A plot of CL_T versus CL_{CR} (Fig. 3) revealed a statistically significant correlation, with a proportional decline in CL_T with decreasing CL_{CR} ($r = 0.70$; $P < 0.0001$). A plot of CL_T versus age (Fig. 4) also revealed a statistically significant correlation, with a general decline in CL_T with an increase in age ($r = -0.73$, $P < 0.0001$).

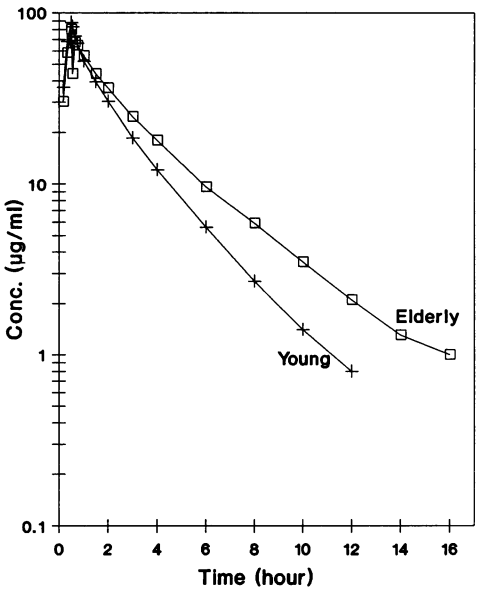

FIG. 1. Mean plasma cefepime concentrations after administration of a 1,000-mg intravenous dose to young and elderly female subjects.

DISCUSSION

In elderly subjects several determinants of drug disposition, such as glomerular filtration, hepatic and renal blood flow, plasma albumin, and oxidative drug metabolism, are reduced (15, 21, 27). There is an age-related decline in glomerular filtration rate of about 35% between ages 25 and 65 years (26) and a reduction of 40 to 50% in hepatic blood flow (13). In addition, there are increases in adipose tissue as a fraction of body weight in 9 to 35% of men and 33 to 49% of women, with a concomitant reduction in lean mass and body water (10, 11).

The data from the present study revealed age- and gender-related differences in the pharmacokinetics of cefepime. The pharmacokinetic parameters in the healthy young male subjects were consistent with those reported previously (2, 3, 7). The pharmacokinetic parameter values for the young male control group are thus representative and could serve as a basis for comparison in the assessment of age- and gender-related changes in cefepime pharmacokinetics. Analysis of the disposition of cefepime revealed apparent age-related alterations in pharmacokinetics which are in agreement with

TABLE 1. Demographic data and pharmacokinetic parameters for a single 1,000-mg intravenous dose of cefepime in young and elderly male and female normal subjects[a]

Subject group	Demographic data			Pharmacokinetic parameters						
	Age (yr)	Body wt (kg)	CL_{CR} (ml/min/kg)	C_{max} (μg/ml)	$t_{1/2}$ (h)	$MRT_{i.v.}$ (h)	$AUC_{0-\infty}$ (μg · h/ml)	CL_T (ml/min/kg)	CL_R (ml/min/kg)	V_{ss} (liter/kg)
Young male	30 ± 6	75 ± 10	1.15 ± 0.19	75.1 ± 9.7	2.26 ± 0.51	2.32 ± 0.30	149 ± 21	1.54 ± 0.22	1.44 ± 0.27	0.21 ± 0.02
Young female	33 ± 5	64 ± 10	1.41 ± 0.21	90.1 ± 17.8	2.15 ± 0.33	2.24 ± 0.36	172 ± 21	1.56 ± 0.22	1.39 ± 0.24	0.21 ± 0.02
Elderly male	67 ± 2	77 ± 9	0.97 ± 0.14	74.4 ± 11.9	3.05 ± 0.50	3.50 ± 0.45	199 ± 30	1.11 ± 0.12	1.03 ± 0.15	0.23 ± 0.03
Elderly female	69 ± 5	65 ± 9	1.19 ± 0.46	83.5 ± 11.9	2.92 ± 0.38	3.30 ± 0.80	218 ± 32	1.22 ± 0.19	0.99 ± 0.16	0.24 ± 0.06
Statistical comparison[b]		M > F	Y > E	M < F	Y < E	Y < E	M < F, Y < E	Y > E	Y > E	Y < E

[a] Data are means ± standard deviations.
[b] M, male; F, female; Y, young; E, elderly.

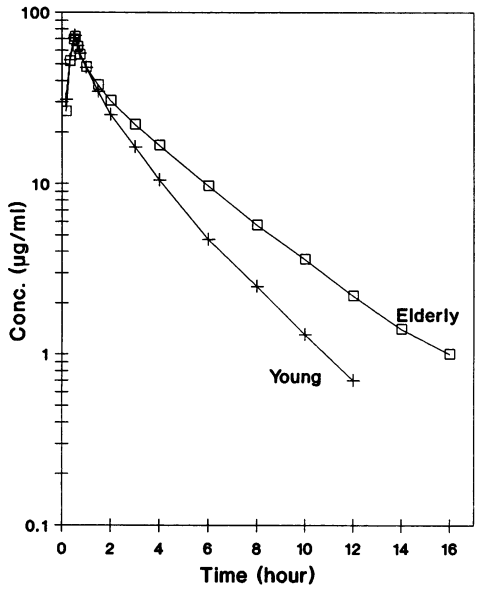

FIG. 2. Mean plasma cefepime concentrations after administration of a 1,000-mg intravenous dose to young and elderly male subjects.

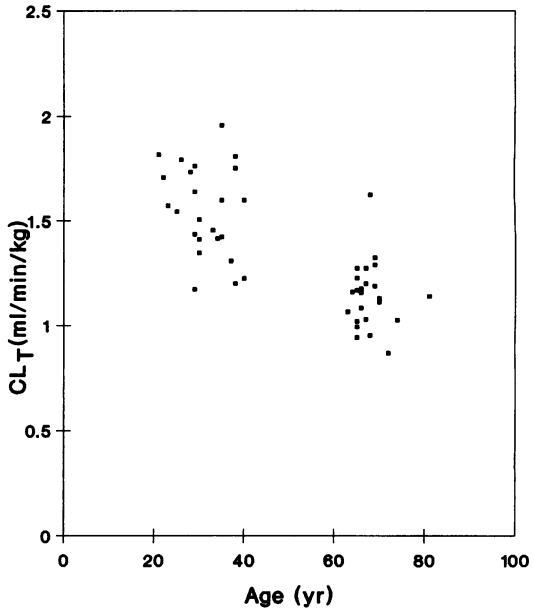

FIG. 4. Relationship between the CL_T of cefepime and age (CL_{CR}) ($r = -0.73$; $P < 0.0001$).

earlier studies on other broad-spectrum cephalosporins and other antibiotics which are primarily excreted unchanged in urine (1, 9, 20, 22, 29). The values for CL_T and CL_R of cefepime were significantly reduced in the elderly subjects when they were compared with those observed in young subjects. The age-related reduction in clearance of cefepime resulted in a statistically significant 1.5-fold increase in $t_{1/2}$ and MRT. Urinary recovery of cefepime accounted for over 80% of the administered dose and was invariant with respect to age or gender. The C_{max} of cefepime was significantly higher in women than it was in men. Since the administered dose was fixed (1,000 mg) and women were lighter in weight than men, this was an expected finding. The values for $t_{1/2}$, CL_T, CL_R, and V_{ss} in female subjects were not significantly different from those observed in male volunteers. These data are consistent with those observed for cefotaxime (16) and cefodizime (17). The decrease in the CL_T of cefepime in elderly subjects is directly related to a decrease in CL_{CR} (Fig. 3). A similar relationship was observed in the recently concluded study of cefepime in subjects with various degrees of renal impairment (5). Although a significant relationship was observed between age and CL_{CR} for subjects participating in the present study, it is not readily apparent whether the age-related changes in the disposition of cefepime are due to the changes in renal function, the increase in age, or some combination of the two processes.

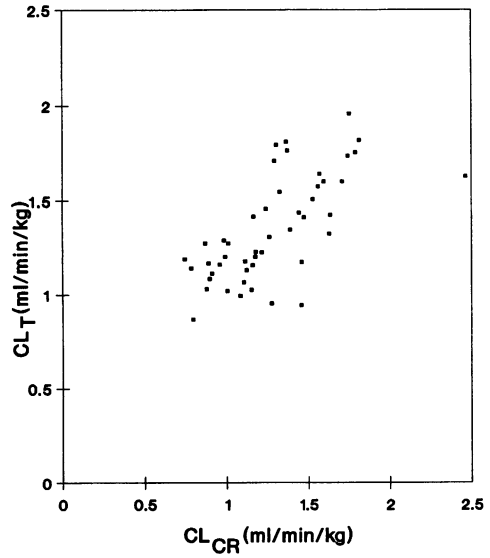

FIG. 3. Relationship between the CL_T of cefepime and CL_{CR} ($r = 0.70$; $P < 0.0001$).

Cefepime is a fourth-generation, broad-spectrum cephalosporin. Since there are no significant differences between males and females for the clearance and volume of distribution parameters, the dosage regimen of cefepime should be independent of gender for the treatment of a given infection. It is administered every 8 to 12 h for the treatment of most infections caused by susceptible bacteria. The mean elimination $t_{1/2}$ was about 3 h in healthy elderly subjects, which was only a small increase from the 2.2-h $t_{1/2}$ observed in young subjects. Such a small increase in $t_{1/2}$ in elderly subjects with normal renal function is not expected to cause the accumulation of cefepime when it is administered two or three times daily. Although the systemic exposure of the elderly subjects to cefepime is greater, it is noteworthy that single doses of 1,000 mg of this cephalosporin were well tolerated by the elderly subjects. Considering the outstanding safety and tolerance profiles of cephalosporin antibiotics in general, and of cefepime in particular, a dosage adjustment of cefepime is not necessary in elderly patients with normal kidney function for their age.

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REFERENCES

1. **Balant, L., P. Dayer, and R. Auckenthaler.** 1985. Clinical pharmacokinetics of the third generation cephalosporins. Clin. Pharmacokinet. **10:**101–143.
2. **Barbhaiya, R. H., S. T. Forgue, C. R. Gleason, C. A. Knupp, K. A. Pittman, D. J. Weidler, and R. R. Martin.** 1990. Safety, tolerance, and pharmacokinetics evaluation of cefepime after administration of single intravenous doses. Antimicrob. Agents Chemother. **34:**1118–1122.
3. **Barbhaiya, R. H., S. T. Forgue, C. R. Gleason, C. A. Knupp, K. A. Pittman, D. J. Weidler, H. Movahhed, J. Tenney, and R. R. Martin.** 1992. Pharmacokinetics of cefepime after single and multiple intravenous administrations in healthy subjects. Antimicrob. Agents Chemother. **36:**552–557.
4. **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.
5. **Barbhaiya, R. H., C. A. Knupp, S. T. Forgue, G. R. Matzke, D. R. P. Guay, and K. A. Pittman.** 1990. Pharmacokinetics of cefepime in subjects with renal insufficiency. Clin. Pharmacol. Ther. **48:**268–276.
6. **Barbhaiya, R. H., C. A. Knupp, S. T. Forgue, G. R. Matzke, C. E. Halstenson, J. A. Opsahl, and K. A. Pittman.** 1991. Disposition of the cephalosporin cefepine in normal and renally impaired subjects. Drug Metab. Dispos. **19:**68–73.
7. **Barbhaiya, R. H., C. A. Knupp, J. Tenney, R. R. Martin, D. J. Weidler, and K. A. Pittman.** 1990. Safety, tolerance and pharmacokinetics of cefepime administered intramuscularly to healthy subjects. J. Clin. Pharmacol. **30:**900–910.
8. **Benet, L. Z., and R. L. Galeazzi.** 1979. Noncompartmental determination of the steady-state volume of distribution. J. Pharm. Sci. **68:**1071–1072.
9. **Blouin, R. A., J. Kneer, and K. Stoeckel.** 1989. Pharmacokinetics of intravenous cefetamet (Ro 15-8074) and oral cefetamet pivoxil (Ro 15-8075) in young and elderly subjects. Antimicrob. Agents Chemother. **33:**291–296.
10. **Bruce, A., M. Andersson, B. Arvidsson, and B. Isaksson.** 1980. Body composition. Prediction of normal body potassium, body water and body fat in adults on the basis of body height, body weight and age. Scand. J. Clin. Lab. Invest. **40:**461–473.
11. **Forbes, G. B., and J. C. Reina.** 1970. Adult lean body mass declines with age: some longitudinal observations. Metabolism **19:**653–663.
12. **Fuchs, P. C., R. N. Jones, A. L. Barry, and C. Thornsberry.** 1985. Evaluation of the in vitro activity of BMY-28142, a new broad-spectrum cephalosporin. Antimicrob. Agents Chemother. **27:**679–682.
13. **Geokas, M. C., and B. J. Haverback.** 1969. The aging gastrointestinal tract. Am. J. Surg. **117:**881–892.
14. **Gibaldi, M., and D. Perrier (ed.).** 1982. Pharmacokinetics, 2nd ed., p. 409–417. Marcel Dekker, Inc., New York.
15. **Greenblatt, D. J., E. M. Sellers, and R. I. Shader.** 1982. Drug disposition in old age. N. Engl. J. Med. **306:**1081–1088.
16. **Guay, D. R. P., G. R. Matzke, K. L. Heim, C. E. Halstenson, P. A. Abraham, and W. F. Keane.** 1987. Influence of gender on the disposition of cefotaxime and desacetylcefotaxime. Ther. Drug Monit. **9:**259–262.
17. **Jonkman, J. H. G., A. Reinberg, B. Oosterhuis, O. E. de Noord, F. A. Kerkhof, Y. Motohashi, F. Levi, F. Dammacco, and F. Carandente.** 1988. Dosing time and sex-related differences in the pharmacokinetics of cefodizime and in the circadian cortisol rhythm. Chronobiologia **15:**89–102.
18. **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.
19. **Kim, K. S., and A. S. Bayer.** 1985. Efficacy of BMY-28142 in experimental bacteremia and meningitis caused by *Escherichia coli* and group B streptococci. Antimicrob. Agents Chemother. **28:**51–54.
20. **Ljungberg, B., and I. Nilsson-Ehle.** 1988. Influence of age on the pharmacokinetics of ceftazidime in acutely ill, adult patients. Eur. J. Clin. Pharmacol. **34:**173–178.
21. **MacLennan, W. J., P. Martin, and B. J. Mason.** 1977. Protein intake and serum albumin levels in the elderly. Gerontology **23:**360–367.
22. **Matzke, G. R., J. J. Jameson, and C. E. Halstenson.** 1987. Gentamicin disposition in young and elderly patients with various degrees of renal function. J. Clin. Pharmacol. **27:**216–220.
23. **Meyers, B. R., and P. Wilkinson.** 1989. Clinical pharmacokinetics of antibacterial drugs in the elderly. Implications for selection and dosage. Clin. Pharmacokinet. **17:**385–395.
24. **Phelps, D. J., D. D. Carlton, C. A. Farrell, and R. E. Kessler.** 1986. Affinity of cephalosporins for β-lactamases as a factor in antimicrobial efficacy. Antimicrob. Agents Chemother. **29:**845–848.
25. **Riegelman, S., and P. Collier.** 1980. The application of statistical moment theory to the evaluation of *in vivo* dissolution time and absorption time. J. Pharmacokinet. Biopharm. **8:**509–534.
26. **Rowe, J. W., R. Andres, J. D. Tobin, A. H. Norris, and N. W. Shock.** 1976. Age-adjusted standard for creatinine clearance. Ann. Intern. Med. **84:**567–569.
27. **Shand, D. G.** 1982. Biological determinants of altered pharmacokinetics in the elderly. Gerontology **28**(Suppl. 1):8–17.
28. **Tauber, M. G., C. J. Hackbarth, K. G. Scott, M. G. Rusnak, and M. A. Sande.** 1981. New cephalosporins ceftotaxime, cefpimizole, BMY-28142 and HR-810 in experimental pneumeococcal meningitis in rabbits. Antimicrob. Agents Chemother. **27:**340–342.
29. **Trang, J. M., T. P. Monson, B. H. Ackerman, F. L. Underwood, J. T. Manning, and C. L. Kearns.** 1989. Effect of age and renal function on cefonicid pharmacokinetics. Antimicrob. Agents Chemother. **33:**142–146.