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Effect of Age and Renal Function on Cefonicid Pharmacokinetics

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Cefonicid (15 mg/kg) was administered intravenously at a constant rate of infusion over 15 min to 10 geriatric patients (mean age, 77 years) and to 4 young subjects (mean age, 35 years). Model-dependent and noncompartmental pharmacokinetic parameters were calculated and found to be congruous; noncompartmental data are reported. Significant differences in the values for area under the curve, mean residence time, total body clearance, and renal clearance were observed between the geriatric and young groups. Mean elimination half-life values were 9.59 and 4.88 h for the geriatric and young groups, respectively. Total body and renal clearances were inversely correlated to age and directly correlated to creatinine clearance. Free fraction was not correlated to albumin concentration but was correlated exponentially to total cefonicid concentration. Despite the prolonged half-life values observed in our geriatric patients, the difference in mean trough concentrations was slight. Daily administration of a 15-mg/kg dose should provide adequate concentrations in serum and should not produce appreciable accumulation in geriatric patients.

Cefonicid is a broad-spectrum, β-lactamase-stable cephalosporin for parenteral administration. It is active against many gram-positive and gram-negative organisms and is indicated for the treatment of infections caused by susceptible pathogens. Cefonicid has been used to treat urinary tract infections, bone and joint infections, skin and skin structure infections, lower respiratory tract infections, and septicemia (9). In healthy adult male volunteers with normal renal function, it exhibits a biexponential concentration in serum versus time curve with an elimination half-life ($t_{1/2}$) of approximately 4.4 h (3). Cefonicid is approximately 98% bound to plasma proteins at drug concentrations in serum between 50 and 20 μg/ml and has a smaller apparent volume of distribution than other broad-spectrum cephalosporins (3, 8).

While several studies have reported the pharmacokinetic data for cefonicid in patients with various degrees of renal dysfunction, no investigations have been conducted in other patient subpopulations (e.g., pediatric, geriatric, or hypoalbuminemic patients) that may exhibit unusual or unique pharmacokinetic characteristics (2, 5, 17). Since glomerular filtration rate, hepatic and renal blood flow, plasma albumin, and oxidative drug metabolism are reduced in geriatric subjects (12, 14, 18), our goal was to determine the effects of age on the pharmacokinetics of cefonicid.

MATERIALS AND METHODS

Subjects. Ten geriatric male subjects ranging in age from 66 to 89 years (mean, 77 ± 8.5 years) were enrolled in this open study after admission to the Veterans Administration Hospital and diagnosis of a urinary tract infection caused by pathogens susceptible to cephalosporins. Four young, nonhospitalized male subjects ranging in age from 30 to 37 years (mean, 34.5 ± 3.1 years) served as controls. Upon admission, a panel of laboratory tests consisting of a complete blood cell count; serum sodium, potassium, chloride, bicarbonate, calcium, phosphate, and creatinine; blood urea nitrogen; liver function tests; and urinalysis was obtained. Any subjects with the following characteristics were excluded from the study: serum creatinine > 1.5 mg/dl; serum albumin < 3 g/dl; known or suspected hypersensitivity to penicillins or cephalosporins; major organ abnormality; and/or malignancy. All geriatric patients had symptomatic bacteriuria with culture isolates reported susceptible to cephalosporins. Informed consent was obtained in accordance with the guidelines of the Human Research Advisory Committee of the University of Arkansas for Medical Sciences and the Human Use Committee of the Veterans Administration Hospital.

Drug administration and sample collection. After being reconstituted with sterile water for injection, a 15-mg/kg dose of cefonicid was diluted in 15 ml of glucose 5% in water and administered as a constant-rate intravenous infusion over 15 min. Thirteen venous blood samples (3 ml) were collected, from a contralateral extremity as follows: before the infusion was started, approximately midway through the infusion (0.133 h), and at 0.263, 0.333, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 16, and 24 h after the beginning of the infusion. Additional 3-ml blood samples were obtained at 0.5, 4, and 12 h for protein-binding determination. Blood samples were collected into glass tubes not containing anticoagulant and were permitted to clot at room temperature. The samples were centrifuged at 2,000 × *g* for 10 min and the serum was harvested and frozen at −70°C until the assay was performed. Spontaneously voided urine samples were collected before drug administration and the following times after drug infusion: 0 to 4, 4 to 8, 8 to 16, and 16 to 24 h. After the urine volume and pH were recorded, the samples were mixed thoroughly and 10-ml aliquots were frozen promptly at −70°C until the analysis was done.

Cefonicid assay. Cefonicid concentrations in serum, protein binding, and urine samples were analyzed by a modification of a method developed in our laboratory (F. L. Underwood and J. M. Trang, 133rd Nat. Meet. Am. Pharm. Assoc. **16**:144, 1986). After the addition of internal standard (cephalothin) to the serum samples, cefonicid and cephalothin were separated by using acetonitrile precipitation and methylene chloride phase separation. Serum samples for

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protein-binding determinations were prepared by membrane centrifugation using disposable ultrafiltration devices (Amicon Corp., Danvers, Mass.). Urine samples were filtered and diluted fivefold in a phosphate buffer (pH 7.4) prior to addition of the internal standard and direct injection into the chromatograph. Chromatography was accomplished by using a reversed-phase C-18 (5 μm) analytical column and an automated high-pressure liquid chromatography system (Waters Associates, Inc., Milford, Mass.). The mobile phase for serum samples and protein-binding determinations was composed of 0.05 M sodium acetate buffer and methanol (67:33). The mobile-phase composition for urine samples was 0.05 M sodium acetate buffer and methanol (69:31). Tetrabutylammonium hydroxide was added to the acetate buffer as an ion-pairing agent, and the pH of the mobile phase was adjusted to 5.1. A flow rate of 2.0 ml/min was used, and the eluate was monitored at 270 nm. Four sets of calibration curves (n = 5 in each set) were constructed; two for serum (5 to 100 μg/ml and 50 to 500 μg/ml), one for serum ultrafiltrate (0.5 to 20 μg/ml), and one for urine (50 to 500 μg/ml). Cefonicid concentrations for all samples were determined by peak area ratio comparison. Within- and between-day reproducibility studies over the entire range of concentrations resulted in coefficients of variation consistently less than 10%. Calculated concentrations were 96.7% of the theoretical concentration for the within-day studies and 95.5% of the theoretical concentrations for the between-day studies. Frozen stability of cefonicid was documented through 30 days.

Pharmacokinetic evaluation. The data for cefonicid concentration in serum were plotted and subjected to model-dependent and noncompartmental analyses. Initial polyexponential parameter estimates were obtained from ESTRIP (6), and final parameter estimates were determined by using KINONITE/BAS (15). Determination of the most appropriate model was evaluated by inspection and comparison of the F statistic and r^2 value from ESTRIP. The following model-dependent pharmacokinetic parameters were calculated with appropriate corrections applied for infusion time: terminal elimination rate constant, elimination half-life ($t_{1/2}$), area under curve of drug concentration in serum versus time (AUC), apparent volume of distribution, and total body clearance (CL) (11, 13). The following parameters were determined by noncompartmental methods: mean residence time (MRT), $t_{1/2}$, apparent steady-state volume of distribution (V_{ss}), CL, and renal clearance (CL_R) (4, 20). No significant differences were found on comparison of model-dependent and noncompartmental pharmacokinetic parameters. Unless otherwise noted, noncompartmental parameters are reported.

Statistical analysis. All grouped data are presented as mean ± standard deviation. Covariance between demographic and pharmacokinetic parameters was evaluated by using linear, least-squares regression analysis. To test for significant differences between grouped pharmacokinetic parameters, an unpaired, two-tailed Student's t test was performed. A probability of <0.05 was selected as the required value for significance. All statistical analyses followed methods outlined by Dixon and Massey (7) or Snedecor and Cochran (19).

RESULTS

Demographic data for all subjects are summarized in Table 1. All subjects were males, with geriatric patients ranging from 66 to 89 years of age (mean, 77.0 ± 8.5 years) and young control subjects ranging from 30 to 37 years of age (mean, 34.5 ± 3.1 years). Significant differences were observed between the values for serum albumin (P = 0.00121) and creatine clearance (P = 0.00215) in the geriatric and young groups. As anticipated, a 55% percent decrease in renal function was observed in the geriatric subjects (12, 18).

TABLE 1. Characteristics of geriatric patients (n = 10) and young subjects (n = 4)

Age group and statistic	Age (yr)	Wt (kg)	Ht (cm)	Body surface area (m^2)	Plasma albumin (g/dl)	Serum creatinine (mg/dl)	Creatinine clearance (ml/min)
Geriatric							
Mean	77.0	62	173	1.74	3.6	1.2	44[a]
SD	8.5	11	6	0.14	0.4	0.2	24
Young							
Mean	34.5	74	180	1.93	4.4	1.1	111
SD	3.1	12	8	0.18	0.1	0.1	33
P		NS[b]	NS	NS	0.00121	NS	0.00215

[a] Incomplete urine collections in subjects 1, 2, and 5; the data for these subjects were not included in the mean.
[b] NS, Not significant.

Figure 1 shows the mean cefonicid concentrations in serum in the geriatric patients and young subjects after a single intravenous dose (15 mg/kg). Mean drug concentrations in serum in both geriatric and young subjects immediately following the infusion (202.36 and 199.04 μg/ml, respectively) were not significantly different, nor were the mean drug concentrations in serum after cefonicid distribution at 1 h (135.95 and 124.01 μg/ml, respectively). However, the mean concentrations in serum from the 6- through the 24-h samples were significantly higher in the geriatric patients ($P < 0.05$).

Noncompartmental pharmacokinetic parameters are presented in Table 2. Comparison of the data from geriatric patients and young subjects revealed significant age-related differences for AUC, MRT, V_{ss} (in liters), and CL. Both AUC and MRT were approximately two times larger in the geriatric group. The mean V_{ss}, CL, and $t_{1/2}$ for the geriatric

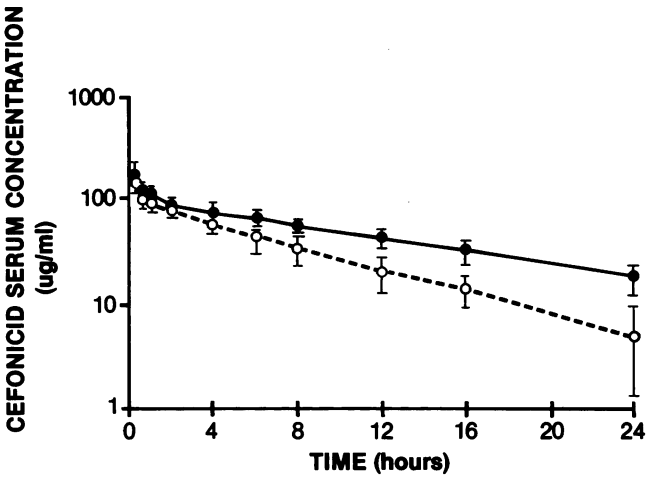

FIG. 1. Cefonicid concentrations in serum in geriatric patients (n = 10) (●) and young subjects (n = 4) (○) versus time after a single 15-mg/kg intravenous dose infused over 15 min. Data shown are mean ± standard deviation.

TABLE 2. Cefonicid noncompartmental pharmacokinetic parameters in geriatric patients (n = 10) and young subjects (n = 4) after a 15-min constant intravenous infusion of the 15-mg/kg dose

Age group and statistic	AUC (μg · h/ml)	MRT (h)	$t_{1/2}$ (h)	V_{ss} (liters)	V_{ss} (liter/kg)	CL (liter/h)	CL_R (ml/min)	% Excreted
Geriatric								
Mean	1,666	13.83	9.59	7.60	0.125	0.560	10.8[a]	97
SD	294	7.51		1.33	0.014	0.106	4.6	37
Young								
Mean	886	7.69	4.88	9.29	0.127	1.318	21.8	93
SD	205	2.55		0.88	0.024	0.292	7.7	19
P	0.00043	0.00141		0.03903	NS[b]	0.00001	0.01421	NS

[a] Incomplete urine collections in subjects 1, 2, and 5; the data for these subjects were not included in the mean.
[b] NS, Not significant.

patients and young subjects were 7.6 and 9.3 liters, 0.560 and 1.318 liters/h, and 9.6 and 4.9 h, respectively. In contrast, the mean V_{ss} was not significantly different when normalized to body weight (0.125 and 0.127 liter/kg for geriatric patients and young subjects, respectively). No correlation was observed between CL and total body weight, therefore CL values were not normalized to kilogram of body weight. Clearance determinations in both liters per hour and milliliters per minute were made to facilitate comparisons to creatinine clearance and other studies. Cefonicid CL was inversely correlated with subject age (r = −0.89324, P = 0.00002 [Fig. 2]) and linearly correlated with creatinine clearance (r = 0.89582, P = 0.00019).

Urine collections were incomplete in 3 geriatric patients, resulting in evaluation of cefonicid renal clearance in 7 of the 10 geriatric subjects. Large variability in urinary excretion data was demonstrated by a wide range in the percent dose excreted. The mean percents dose excreted unchanged in the urine for geriatric and young subjects with complete urine collections were 97 and 93%, respectively. The mean values of CL_R, based upon data from subjects with complete collections, were 10.8 and 21.8 ml/min in the geriatric and young groups, respectively (P = 0.01421). As with CL, no correlation was observed between CL_R and body weight. Similarly, cefonicid CL_R was inversely correlated with subject age (r = −0.78705, P = 0.00404) and directly correlated with creatinine clearance (r = 0.82984, P = 0.00157 [Fig. 3]).

Plasma protein-binding data for cefonicid are summarized in Table 3. Protein-binding data in subject 9 were greater than five times the standard deviation different than the mean at each time point and not included in the statistical analyses. This patient was receiving phenytoin during the study, which could have altered the protein binding of cefonicid to albumin. The mean free fraction in the geriatric group at 0.5 h was significantly higher than that observed in the young control group (0.147 and 0.070, respectively). In contrast, the mean values of the free fraction at 4 h for the geriatric patients and young subjects were not significantly different (0.036 and 0.031, respectively). No comparisons of the free fraction at 12 h could be made, since the free cefonicid concentration in the young subjects was consistently below the analytical limits of detection. A decrease in the free fraction was observed in the geriatric group at 0.5, 4, and 12 h after drug administration, as the total and free cefonicid concentrations decreased, corresponding to increases in the mean percent protein bound of 87.8, 96.7, and 96.9% at these times. Similarly, the mean percent protein bound in the young subjects increased from 93.0 to 96.9% at 0.5 and 4 h, respectively. Regression analyses of free fraction versus total cefonicid concentration data revealed a significant exponential correlation (r = 0.64542, P < 0.0002 [Fig. 4]).

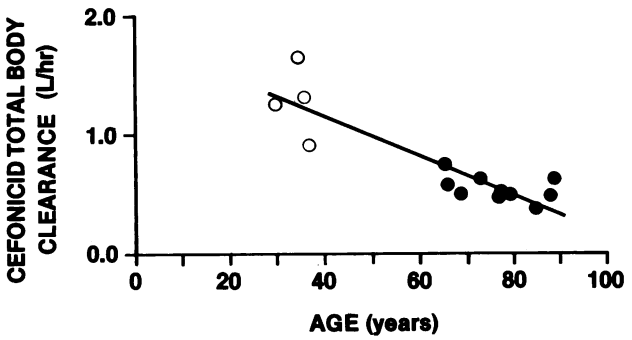

FIG. 2. Relationship between cefonicid CL and age in geriatric patients (n = 10) (●) and young subjects (n = 4) (○). CL = 1.8468 − (0.0165 × age); r = −0.89324, P = 0.00002.

DISCUSSION

Our analysis of cefonicid disposition revealed apparent age-related pharmacokinetic differences which are in agree-

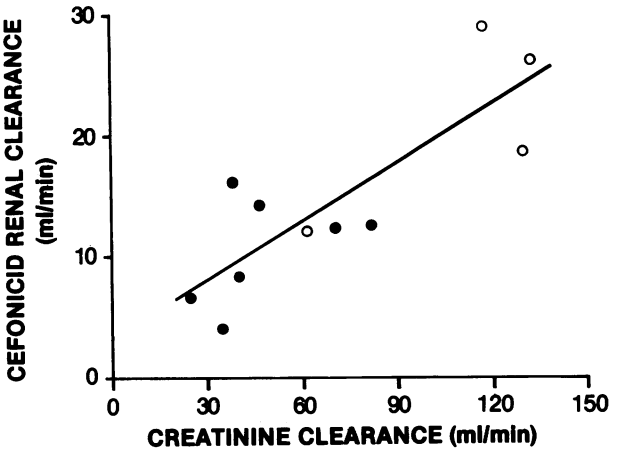

FIG. 3. Relationship between cefonicid CL_R and creatinine clearance in geriatric patients (n = 7) (●) and young subjects (n = 4) (○). CL_R = 3.1324 + (0.1634 × CL_{CR}), where CL_{CR} is creatinine clearance; r = 0.82984, P = 0.00157.

TABLE 3. Free cefonicid concentrations in serum and free fractions in elderly patients (n = 9) and young subjects (n = 4) after a 15-min constant intravenous infusion of a 15-mg/kg dose

Age group and statistic	0.5-h sample		4-h sample		12-h sample	
	Free concn (μg/ml)	Free fraction	Free concn (μg/ml)	Free fraction	Free concn (μg/ml)	Free fraction
Geriatric						
Mean	22.54[a]	0.147[a]	2.63	0.036	1.46	0.034
SD	16.09	0.085	0.85	0.016	0.45	0.016
Young						
Mean	9.76	0.070	2.03	0.031		
SD	0.98	0.010	0.35	0.003		
P	NS[b]	0.03859	NS	NS		

[a] Intravenous infusion infiltrated in patient 4; resulting free concentration and free fraction at 0.05 h were not included in statistical analyses.
[b] NS, Not significant.

ment with earlier studies (12, 18). The similar V_{ss} (liters/kg) in our geriatric patients and young subjects is consistent with the known distribution characteristics of highly protein-bound drugs, with distribution volumes limited to vascular and interstitial fluids. The values for CL and CL_R of cefonicid in our geriatric patients were reduced by 58 and 51%, respectively, corresponding to the age-related reduction in creatinine clearance. The reduced CL resulted in an approximate twofold increase in MRT and $t_{1/2}$ in the geriatric patients and a fourfold increase in cefonicid concentration in serum at 24 h.

The cefonicid pharmacokinetic parameters in our young subjects are consistent with those previously reported (16, 17), indicating that our control group (n = 4) provided representative values for cefonicid pharmacokinetic parameters for comparison with those of our geriatric group. Mean peak concentrations in serum after administration of 1 g have been reported to range from 148 to 221 μg/ml (16, 17). Mean peak drug concentrations in serum observed in both our geriatric patients and young subjects (202 and 199 μg/ml, respectively) after a comparable dose (15 mg/kg) were similar to these values. The mean V_{ss} observed in our geriatric patients and young subjects (0.125 and 0.127 liter/kg, respectively) are also in agreement with reported values (0.11 to 0.13 liter/kg) (1, 3). In contrast, the mean CL observed in our geriatric patients (0.562 liter/h or 9.3 ml/min) is substantially less than the values observed in our young subjects (1.325 liters/h or 22.1 ml/min) and those reported previously in other healthy adult populations (21.7 to 27.1 ml/min) (3, 17).

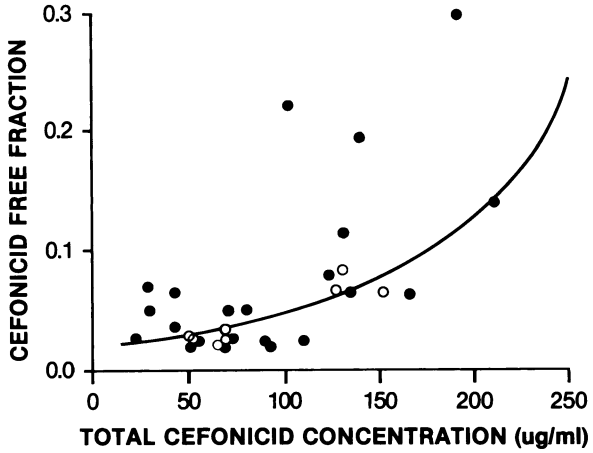

FIG. 4. Relationship between cefonicid free fraction and total cefonicid concentration in serum in geriatric patients (n = 10) (●) and young subjects (n = 4) (○). ff = 0.01977 × Exp(0.00966 × C), where ff is the cefonicid free fraction and C is the total cefonicid concentration in serum; r = 0.64642, P < 0.0002.

The mean free fraction in our geriatric and young subjects at 4 h (0.034 and 0.031, respectively) were comparable with the values (approximately 0.02) reported for patients with total cefonicid concentrations in serum of 20 to 50 μg/ml (8). However, the mean free fraction in our geriatric group at 0.5 h was approximately twice that observed in the young group (0.144 and 0.070, respectively). In addition, the mean free fraction in the geriatric group at 0.5 h was fourfold higher than that observed at either 4 or 12 h, indicating possible concentration-dependent, nonlinear binding of cefonicid at total concentrations greater than approximately 100 μg/ml. These findings are in agreement with those of Dudley et al. (10).

It is important to note that our geriatric subjects were hospitalized patients with infections and limited ambulatory activity. However, none of our geriatric patients had body temperatures in excess of 38°C and none had any major organ abnormality that would be expected to influence cefonicid disposition. It is unlikely therefore, that the observed differences in CL and $t_{1/2}$ were related to the infectious process. This is also supported by the similar V_{ss} values (in liters per kilogram) observed in our geriatric patients and young subjects. In contrast, the decreased CL appears to be related to an age-related decrease in renal function as supported by the direct proportional relationship to creatinine clearance (r = 0.89582, P = 0.00019). Our data agree well with those reported by Blair et al. (5), who demonstrated a similar relationship in nongeriatric patients with various degrees of renal compromise.

Despite the prolonged $t_{1/2}$ observed in our geriatric patients and an approximate fourfold increase in mean trough cefonicid concentration (19.6 versus 5.1 μg/ml in young subjects), daily administration of a 15-mg/kg dose should not produce excessive accumulation of cefonicid in geriatric patients with normal renal function for their age. Trough concentrations in serum of >25 μg/ml would not be expected in these patients. Since the cephalosporins have a wide therapeutic index, an elevation in the trough concentration in serum of this magnitude would not be expected to cause any untoward effects. On the basis of our data, it is suggested that a cefonicid dose of 15 mg/kg every 24 h should provide adequate drug concentrations in serum in geriatric patients with creatinine clearance values similar to those observed in our study.

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