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Crossover Assessment of Serum Bactericidal Activity and Pharmacokinetics of Five Broad-Spectrum Cephalosporins in the Elderly

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To better define the pharmacokinetics and serum bactericidal activity (SBA) of the expanded-spectrum cephalosporins in the elderly, we administered single 2-g intravenous infusions of cefoperazone, cefotaxime, ceftriaxone, ceftazidime, and ceftizoxime to six healthy volunteers over the age of 65 years. Serum was collected over 24 h, and concentrations were determined by high-performance liquid chromatography; pharmacokinetic parameters were determined for each drug. SBA was measured against representative strains of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, and *Pseudomonas aeruginosa*. All agents tested had excellent SBAs against *E. coli* and *K. pneumoniae*, often for a longer duration than would be expected on the basis of conventional dosing regimens. Ceftazidime had the greatest SBA against *E. aerogenes* and was the only agent with a substantial SBA against *P. aeruginosa*. Although ceftizoxime had the greatest SBA against *S. aureus*, none of these cephalosporins had substantial antistaphylococcal SBAs. Pharmacokinetic analysis revealed that cefoperazone and ceftriaxone had markedly different concentration-time profiles in the elderly volunteers than would have been expected on the basis of existing data from younger volunteers. For older patients, dosing guidelines for these two agents may need to be altered.

The broad-spectrum cephalosporins cefoperazone, cefotaxime, ceftriaxone, ceftazidime, and ceftizoxime are administered commonly to elderly patients. Although the pharmacokinetics of these cephalosporins have been well studied (1), there have been no crossover pharmacokinetic trials in the elderly.

Conventional in vitro susceptibility tests measure only inhibitory antimicrobial activity under standard laboratory conditions. An alternative to conventional susceptibility tests, the serum bactericidal test (SBT), may provide a more meaningful measure of the potential usefulness of antimicrobial agents (7, 22, 43, 47, 52–54). The SBT takes into consideration the achievable concentration of the antimicrobial agent in serum as well as its inherent antibacterial activity, and guidelines for a standard test method have been published recently (35). In studies in which serum bactericidal testing has been used in young volunteers, differences in the broad-spectrum cephalosporins have been shown, including pharmacokinetics, in vitro activity, and serum bactericidal activity (SBA) (3, 4, 15, 17, 18, 23, 38, 49, 50). Although elderly individuals may exhibit altered metabolism and pharmacokinetics of these antimicrobial agents (1, 19, 21, 24, 26, 27, 31–33, 42), no studies of SBA have been done in this population. Therefore, we administered single 2-g doses of cefoperazone, cefotaxime, ceftriaxone, ceftazidime, and ceftizoxime to six healthy elderly volunteers and studied both the pharmacokinetics and SBAs of these agents.

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MATERIALS AND METHODS

Study subjects. Six healthy elderly volunteers (three males, three females) participated in the study. They had the following characteristics (means ± standard deviations): age, 70.7 ± 3.5 years; height, 165.0 ± 8.6 cm; weight, 74.6 ± 16.3 kg; body surface area, 1.82 ± 0.21 m^2; serum creatinine, 1.0 ± 0.3 mg/dl; calculated creatinine clearance, 55.9 ± 13.5 ml/min per 1.73 m^2. Informed consent was obtained from all subjects, and all subjects were requested to refrain from ingesting alcohol or caffeine 24 h before and during each study day. A medical history, physical examination, and a panel of laboratory tests consisting of serum chemistries, complete blood cell and platelet counts, and urinalysis were performed before and after the study. All laboratory results were normal, and physical examination showed no change during or following completion of the study.

Antimicrobial agents. Each subject received a single 2-g dose of each antimicrobial agent in a randomized crossover fashion at weekly or greater intervals. The cephalosporins cefoperazone, cefotaxime, ceftriaxone, ceftazidime, and ceftizoxime were reconstituted and diluted to a total volume of 50 ml with sterile water for injection and then infused over 30 min into a peripheral vein in the arm with a constant-rate infusion pump. Standard analytical powders were provided by the manufacturer of each antimicrobial agent and were used for determination of MICs and MBCs as well as for concentration analysis controls.

Clinical parameters. Ideal body weight was calculated by the following formulas: 45.5 + 2.3 kg for every inch (2.54 cm) over 5 ft (1.524 m) for females and 50 + 2.3 kg for every inch (2.54 cm) over 5 ft (1.524 m) for males (11). Body surface area was determined from a table derived by the method of DuBois and DuBois (14). Creatinine clearance

was calculated from the formula of Cockcroft and Gault (6) and normalized to 1.73 m^2 of body surface area.

Specimen collection. Blood samples (8 ml) for measurement of SBA and drug concentration were obtained before the infusion (blank); just after the end of the infusion (0.5 h); and 1, 2, 4, 8, 12, and 24 h after the start of the infusion. Samples were placed immediately on ice and centrifuged, and the serum was harvested. All samples were kept frozen at −70°C until they were analyzed.

Concentration analysis. The cephalosporin concentrations were determined by specific high-performance liquid chromatography techniques that were modified from assays described previously (29, 44, 48). Briefly, 0.5-ml serum samples were combined with an ice-cold 0.5-ml portion of a mixture containing 70% methanol, 30% 0.1 M sodium acetate (pH 5.2), and internal standard. This mixture was vortexed for 30 s and then incubated at −20°C for 10 min. The specimens were centrifuged (1,500 × *g*) for 10 min, and 15 μl of the resultant supernatant was injected onto the column. For cefoperazone the internal standard was ceftriaxone (100 μg/ml), for cefotaxime the internal standard was cefoperazone (100 μg/ml), for ceftriaxone the internal standard was cefoperazone (100 μg/ml), for ceftazidime the internal standard was cefotaxime (50 μg/ml), and for ceftizoxime the internal standard was cefotaxime (50 μg/ml).

Chromatography was performed at ambient temperature by using equipment from Waters Associaties, Inc. (Milford, Mass.): a model 510 pump, a model 712 intelligent sample processor, a C-18 10-μm Guard-PAK precolumn, C-18 10-μm (3.9 mm by 30 cm) μBondapak column, a model 490 UV detector set at a wavelength of 254 nm, and a model 730 integrator. For cefoperazone, cefotaxime, and ceftriaxone, an aqueous-organic mobile phase consisted of 10 mM phosphate buffer (pH 7.5) which contained 10 mM hexadecyltrimethylammonium bromide–acetonitrile. Aqueous/organic phase ratios (vol/vol) and mobile phase flow rates varied and were 75/25 at 1.3 ml/min for cefoperazone, 82/18 at 2.0 ml/min for cefotaxime, and 65/35 at 1.2 ml/min for ceftriaxone. For ceftazidime and ceftizoxime, 1,000 ml of the aqueous-organic mobile phase consisted of 24 ml of glacial acetic acid dissolved in 876 ml of high-performance liquid chromatographic-grade water and 100 ml of acetonitrile, respectively. The mobile phase flow rate was 1.5 ml/min for both drugs.

Cephalosporin concentrations were determined by measuring peak heights relative to those of the appropriate primary drugs and internal standards. The lowest limit of detection was defined as a concentration of less than 0.8 μg/ml. The interday coefficients of variation for each of the cephalosporin assays were as follows: cefoperazone, 5.9%; cefotaxime, 3.6%; ceftriaxone; 3.2%; ceftazidime, 2.1%; and ceftizoxime, 5.3%.

Microorganisms and microbiologic assays. Five microorganisms, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, and *Pseudomonas aeruginosa*, were selected for analysis of SBA. All strains were isolated from bacteremic patients at Robert Wood Johnson University Hospital, New Brunswick, N.J. The MICs and MBCs of the five cephalosporins against each microorganism were determined by the microdilution method established by the National Committee for Clinical Laboratory Standards (NCCLS) (34, 36). The MBCs for each microorganism and drug are shown in Table 1. SBA was determined by using the standardized microdilution method of Reller and Stratton (40) that has been adopted in the proposed guideline published by the NCCLS (35).

TABLE 1. MBCs of broad-spectrum cephalosporins against the study microorganisms

Microorganism	MBC (μg/ml)				
	Cefoperazone	Cefotaxime	Ceftriaxone	Ceftazidime	Ceftizoxime
S. aureus	4	2	4	16	8
E. coli	≤0.06	≤0.06	0.125	≤0.06	≤0.06
K. pneumoniae	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
E. aerogenes	32	8	8	8	≥64
P. aeruginosa	16	32	16	2	32

Pharmacokinetic analysis. For each of the subjects, five cephalosporin serum concentration-versus-time curves were described by a two-compartment model with constant-rate input. The best coefficient of determination, r^2, from the initial JANA stripping of data was used to determine the compartmental analysis (12). The PCNONLIN two-compartment model with constant intravenous input and first-order output algorithm was used for pharmacokinetic parameter determination (46). The data were weighted as $1/y^2$.

The following parameters were calculated: peak concentration in serum, C_{max} (in micrograms per milliliter); volume of distribution in the central compartment, V_1 (in liters/1.73 m^2); elimination and steady-state volumes of distribution, V_{area} (in liters/1.73 m^2) and V_{ss} (in liters/1.73 m^2), respectively; distribution and elimination half-lives, $t_{1/2\alpha}$ (in hours) and $t_{1/2\beta}$ (in hours), respectively; area under serum concentration-time curve, AUC (in μg · h/ml per 1.73 m^2); and total clearance, CL (in ml/min per 1.73 m^2).

Pharmacodynamic analysis. Calculations of SBA were done by assigning each reciprocal bactericidal titer an ordinal number (e.g., <1:2 = 0, 1:2 = 1,. . .1:2,048 = 11). Following the calculations, the results were rounded to the nearest whole number and then reconverted to the corresponding reciprocal serum bactericidal titer. The duration of SBA was defined as the time (in hours) in which an SBA of ≥1:2 could be detected at a given time point.

Statistical analysis. Pharmacokinetic values for each drug were compared by using analysis of variance (41). The Wilcoxon rank sum test was used to evaluate pharmacodynamic values (41). A significant difference was defined as $P < 0.05$.

RESULTS

Pharmacokinetics. All subjects completed the study. Mean concentrations of drug in serum obtained at various times for the five broad-spectrum cephalosporins in the six elderly subjects after administration of single 2-g doses are given in Table 2, and mean serum concentration-time profiles of the five drugs are shown in Fig. 1.

Pharmacokinetic values for these cephalosporins are listed in Table 3. Peak concentrations were significantly higher ($P < 0.05$) for cefoperazone, ceftriaxone, and ceftizoxime than they were for ceftazidime and cefotaxime. Concentrations were detectable at 8 h for cefotaxime; 12 h for ceftizoxime; and 24 h for cefoperazone, ceftriaxone, and ceftazidime. The concentrations were significantly higher ($P < 0.05$) for ceftriaxone than they were for cefoperazone and ceftazidime; two of the six volunteers did not have detectable concentrations of cefoperazone or ceftazidime at 24 h.

The $t_{1/2\beta}$ and AUC were longest and largest, respectively, for cefoperazone and ceftriaxone ($P < 0.05$ for both parameters versus those of the other cephalosporins) and shortest

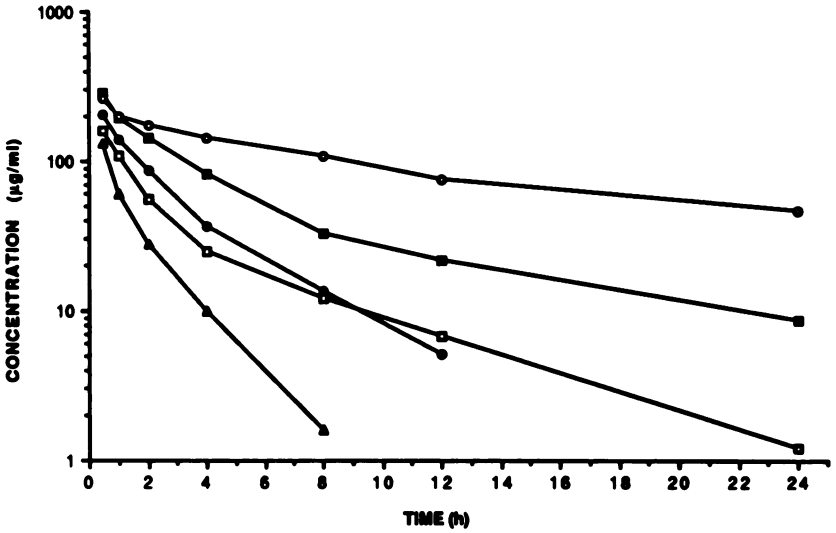

FIG. 1. Crossover mean concentration-time profiles of cefoperazone (■), cefotaxime (▲), ceftriaxone (○), ceftazidime (□), and ceftizoxime (●) in serum from elderly volunteers following the administration of 2-g intravenous infusions over 30 min.

and lowest, respectively, for cefotaxime. Ceftazidime and ceftizoxime had intermediate values for these parameters. Total clearance was greatest for cefotaxime, intermediate for ceftazidime and ceftizoxime, and least for cefoperazone and ceftriaxone. No difference was noted in $t_{1/2\alpha}$, V_1, AUC, and V_{ss} values for the five cephalosporins.

Pharmacodynamics. Mean serum bactericidal titers over time for the five broad-spectrum cephalosporins against the five microorganisms are given in Table 4. These drugs had lower SBAs against *S. aureus*, *E. aerogenes*, and *P. aeruginosa* than they did against *E. coli* and *K. pneumoniae*. Against *S. aureus*, ceftizoxime and cefotaxime had the highest peak SBA (Table 4). The duration of antistaphylococcal SBA was longest for ceftriaxone (24 h) followed by those for cefoperazone (12 h), ceftazidime and ceftizoxime (8 h), and cefotaxime (4 h). Peak SBAs and duration of activity of all the agents were similar against both *E. coli* and *K. pneumoniae*. Mean peak titers of ≥1:1,024 were present for each cephalosporin. Ceftriaxone, ceftazidime, and ceftizoxime had SBAs for at least 24 h after dosing, and cefoperazone and cefotaxime had SBAs for at least 12 h after dosing. Ceftriaxone had considerable activity (titer range, 1:64 to 1:2,048), even at the trough of the usual dosing interval (i.e., every 24 h). Similarly, cefoperazone, ceftazidime, and ceftizoxime had SBAs for all volunteers at the trough of their usual dosing intervals (i.e., 12, 8, and 8 h, respectively), although the level of SBA was not as great as that observed with ceftriaxone. The SBAs of the cephalosporins were

TABLE 2. Concentrations of broad-spectrum cephalosporins in serum from six elderly volunteers

Antimicrobial agent	Mean ± SD concn (µg/ml) at the following times (h):						
	0.5	1.0	2.0	4.0	8.0	12.0	24.0
Cefoperazone	288.9 ± 58.6	194.0 ± 46.3	142.2 ± 40.7	81.6 ± 16.8	33.7 ± 14.5	21.6 ± 13.4	8.8 ± 9.2[a]
Cefotaxime	132.7 ± 33.7	61.4 ± 10.7	28.0 ± 5.5	10.0 ± 2.2	1.6 ± 1.4[b]	ND[c]	ND
Ceftriaxone	261.6 ± 61.6	202.6 ± 58.2	173.5 ± 36.0	141.9 ± 29.8	109.9 ± 28.9	76.8 ± 14.0	47.8 ± 15.0[b]
Ceftazidime	167.3 ± 48.5	101.8 ± 20.9	56.1 ± 10.5	35.8 ± 8.6	13.6 ± 4.6	2.5 ± 1.5	0.2 ± 0.6[a]
Ceftizoxime	205.2 ± 40.9	141.0 ± 27.9	88.0 ± 26.1	37.3 ± 11.8	13.5 ± 2.4	5.1 ± 1.3[b]	ND

[a] $n = 4$; the other two volunteers had concentrations of <0.8 µg/ml.
[b] $n = 6$; all six volunteers had detectable concentrations at 8, 12, and 24 h for cefotaxime, ceftizoxime, and ceftriaxone, respectively.
[c] ND, Not detectable.

TABLE 3. Pharmacokinetic values for the broad-spectrum cephalosporins[a]

Parameter	Cefoperazone	Cefotaxime	Ceftriaxone	Ceftazidime	Ceftizoxime
C_{max} (µg/ml)	288.9 ± 58.6	132.7 ± 33.7	261.6 ± 61.6	167.3 ± 48.5	205.2 ± 40.9
$t_{1/2\alpha}$ (h)	1.50 ± 0.28	0.30 ± 0.13	1.24 ± 1.66	0.48 ± 0.45	0.54 ± 0.22
$t_{1/2\beta}$ (h)	10.3 ± 4.3	2.0 ± 0.8	15.2 ± 3.9	3.7 ± 2.0	3.5 ± 2.1
V_1 (liter/1.73 m^2)	7.1 ± 1.3	10.2 ± 2.7	6.2 ± 1.4	9.4 ± 3.7	7.5 ± 0.9
V_{area} (liter/1.73 m^2)	23.8 ± 8.6	28.4 ± 10.1	13.5 ± 3.0	24.9 ± 14.0	19.4 ± 12.2
V_{ss} (liter/1.73 m^2)	14.7 ± 3.8	20.6 ± 4.0	11.8 ± 1.6	18.1 ± 4.9	14.2 ± 6.8
CL (ml/min per 1.73 m^2)	29.7 ± 11.5	172.3 ± 19.3	10.8 ± 3.3	79.3 ± 13.3	62.5 ± 4.8
AUC (µg · h/ml)	1,215.9 ± 498.9	182.0 ± 21.1	3,144.4 ± 731.9	409.2 ± 62.4	516.4 ± 80.3

[a] Data are expressed as means ± standard deviations.

TABLE 4. SBAs of broad-spectrum cephalosporins

Organism and antimicrobial agent	Median reciprocal serum bactericidal titer at the following times (h)[a]						
	0.5	1	2	4	8	12	24
S. aureus							
Cefoperazone	64	32	32	8	4	2	NA[a]
Cefotaxime	128	32	16	4	NA	NA	NA
Ceftriaxone	32	32	8	8	4	4	2
Ceftazidime	64	16	8	4	2	NA	NA
Ceftizoxime	256	32	16	4	2	NA	NA
E. coli							
Cefoperazone	1,024	1,024	512	1,024	128	32	2
Cefotaxime	2,048	2,048	2,048	512	32	8	NA
Ceftriaxone	1,024	1,024	2,048	2,048	2,048	1,024	256
Ceftazidime	2,048	1,024	1,024	1,024	512	32	4
Ceftizoxime	1,024	2,048	1,024	1,024	512	32	2
K. pneumoniae							
Cefoperazone	1,024	1,024	128	256	64	32	NA
Cefotaxime	1,024	2,048	1,024	512	32	4	NA
Ceftriaxone	2,048	2,048	1,024	1,024	512	512	128
Ceftazidime	2,048	2,048	512	512	128	32	2
Ceftizoxime	2,048	2,048	2,048	1,024	512	128	8
E. aerogenes							
Cefoperazone	8	16	8	4	2	2	<2
Cefotaxime	64	32	4	2	2	NA	NA
Ceftriaxone	64	64	16	32	32	16	4
Ceftazidime	256	128	64	32	8	2	NA
Ceftizoxime	8	4	2	2	<2	NA	NA
P. aeruginosa							
Cefoperazone	8	4	4	2	2	2	<2
Cefotaxime	4	4	2	NA	NA	NA	NA
Ceftriaxone	4	4	2	2	2	2	NA
Ceftazidime	128	64	16	16	4	2	<2
Ceftizoxime	2	2	<2	NA	NA	NA	NA

[a] NA, No activity or the reciprocal serum bactericidal titer was <2.

similar for both *E. aerogenes* and *P. aeruginosa*; for both of these microorganisms, ceftazidime had the greatest peak SBA. Against *E. aerogenes*, peak SBAs of cefotaxime and ceftriaxone were 2-fold less than that of ceftazidime, and the peak SBAs of cefoperazone and ceftizoxime were 16- to 32-fold less than that of ceftazidime (Table 4). The duration of SBA against *E. aerogenes* was longest with ceftriaxone (24 h), followed by cefoperazone and ceftazidime (12 h) and cefotaxime and ceftizoxime (8 h). Against *P. aeruginosa*, ceftazidime had a peak SBA that was 16-fold greater than that of cefoperazone, 32-fold greater than those of cefotaxime and ceftriaxone, and 64-fold greater than that of ceftizoxime.

DISCUSSION

This crossover study measured comparative pharmacokinetics and SBAs of expanded-spectrum cephalosporins in the elderly and demonstrated differences among these agents in both areas. In the elderly volunteers that we studied, some of the pharmacokinetic parameters among the five agents tested, including C_{max}, $t_{1/2\beta}$, CL, and AUC, showed statistically significant differences. In contrast, volumes of distribution (V_1, V_{area}, and V_{ss}) and $t_{1/2\alpha}$ were not significantly different among these drugs.

The pharmacokinetic parameters of ceftriaxone and ceftazidime were within the range of those previously published in noncrossover studies of elderly individuals (13, 19, 20, 24, 27, 28, 33, 39). This is the first published report in which the pharmacokinetics of ceftizoxime in the elderly have been described. In two prior noncrossover studies of cefotaxime in the elderly, in which different drug administration methods and older individuals were studied, different values were reported for the volume of distribution, CL, and AUC, although $t_{1/2\beta}$ was similar to that observed for cefotaxime in this study (31, 32). The results obtained for the pharmacokinetic parameters of cefoperazone examined in our study differed from those in a noncrossover study (30) of the elderly but were similar to results from a cefoperazone-sulbactam study (42) of the elderly. Differences in the results of this and the earlier study of cefoperazone (30) were noted for volumes of distribution, CL, AUC, and $t_{1/2\beta}$ (10.3 h in this study versus 2.2 h in the previous report [30]). The differences cannot be explained. However, the $t_{1/2\beta}$s of the other cephalosporins obtained in our study were not different from those obtained in previously published studies of elderly volunteers (13, 19, 20, 24, 26, 27, 33, 39), emphasizing the importance of a crossover design when comparing cephalosporin pharmacokinetics.

The peak concentrations of all five broad-spectrum cephalosporins in serum had a considerable range, from 132.7 to 288.9 μg/ml. The duration of detectable concentrations in serum also varied; for example, cefotaxime was detectable for 8 h (mean concentration at 8 h 1.4 μg/ml), whereas ceftriaxone was detectable for at least 24 h (mean concen-

tration at 24 h, 57.8 μg/ml). These single 2-g dose concentrations do not take into consideration drug accumulation. Estimation of drug accumulation by a two-compartment intravenous infusion model (16) and calculation of maximum (C_{pssmax}) and minimum (C_{pssmin}) concentrations based on a 30-min infusion and normal dosing intervals showed that C_{pssmax} increased the most for ceftriaxone (mean increase of 62.5 μg/ml when the dose was given every 24 h), with lesser increases noted for the other cephalosporins (range, 0 to 16.6 μg/ml). The calculated C_{pssmin} showed less dramatic increases but surprisingly high values for ceftriaxone (65.2 μg/ml) and cefoperazone (41.1 μg/ml when the dose was given every 12 h) were noted.

The concentration profiles of cefotaxime, ceftazidime, and ceftizoxime in serum were slightly elevated in comparison with the concentrations observed in studies of younger populations; there was also a comparative increase in $t_{1/2\beta}$ and a decrease in CL (9, 21, 23, 28, 37, 45, 51). We speculate that these differences are due to decreased renal clearance in the elderly, since no appreciable changes in volumes of distribution were evident in our volunteers compared with those obtained in previously reported studies of young volunteers (9, 21, 23, 28, 37, 45, 51). From the perspective of pharmacokinetic analysis, the changes in pharmacokinetics seen in older individuals are not substantive enough to warrant major alterations in either dose or dosing intervals for cefotaxime, ceftazidime, or ceftizoxime, although the concentration profile of ceftazidime and ceftizoxime in serum may support dosing every 12 h in some individuals. In contrast, the concentration profiles of ceftriaxone and cefoperazone in our elderly subjects showed marked differences from those of studies of young healthy volunteers (2, 8, 23, 39, 45). The $t_{1/2\beta}$s were significantly longer in the elderly volunteers than in young volunteers for ceftriaxone (15.2 versus 6.5 h) and cefoperazone (10.3 versus 2.2 h), resulting in significantly higher trough concentrations in the elderly at 12 h for cefoperazone and 24 h for ceftriaxone (Table 2). Two factors probably accounted for the difference in concentration-time profiles for ceftriaxone and cefoperazone in elderly versus younger individuals: increased volume of distribution and decreased nonrenal clearance (5, 10, 19, 27, 30). Based on this pharmacokinetic analysis, dosing intervals greater than 12 h for cefoperazone and greater than 24 h for ceftriaxone or a reduction in the dose without a change in the dosing interval may optimize therapy in elderly patients.

When SBAs against the different bacterial organisms were assessed, it became apparent that a wide range of possible dosing intervals could be acceptable. For example, the duration of bactericidal activity for very susceptible microorganisms such as *E. coli* or *K. pneumoniae* revealed that SBAs were present for 12 h in the case of cefotaxime and 24 h in the cases of ceftazidime and ceftizoxime. Thus, longer-than-standard dosing intervals may be acceptable for the treatment of infections caused by such highly susceptible microorganisms. Conversely, SBA results for more resistant microorganisms showed that standard dosing intervals may be inadequate against certain infections (7, 22, 43, 47, 52–54). For example, although ceftriaxone may achieve concentrations is serum well above the MBC for *P. aeruginosa* for 24 h, SBA was minimal 2 h after dosing (Table 4), suggesting that ceftriaxone has little, if any, value as a treatment for serious pseudomonal infections.

An apparent paradox in Tables 1, 2, and 4 requires discussion. The conventional NCCLS method for broth dilution susceptibility testing (34) uses cation-supplemented Mueller-Hinton broth as the diluent, whereas the proposed NCCLS SBT method (35) uses a diluent of cation-supplemented Mueller-Hinton broth mixed in equal parts with human serum. Thus, the total drug concentration is measured in conventional NCCLS broth testing, whereas less than total drug concentration is measured by the NCCLS SBT method (largely because of protein binding) (15, 25, 47). In one example of the apparent paradox, cefoperazone had a greater SBA (1:32) than ceftriaxone (1:8) against *S. aureus* at 2 h, despite the greater total drug concentration of ceftriaxone and the equivalent MBCs of the two drugs. Given the greater protein binding of ceftriaxone and the measurement of predominantly free drug only by the SBT, it is not surprising that ceftriaxone has a lower SBA (15, 25, 47). Other examples (e.g., ceftazidime and ceftriaxone against *E. aerogenes* and cefoperazone and ceftriaxone against *P. aeruginosa*) can be explained in the same manner (15, 25, 47). This apparent paradox is not as evident for *E. coli* and *K. pneumoniae*. The work of Leggett and Craig (25) has suggested that the effect of protein binding is reduced for these organisms, possibly because of bacterial inhibitory factors in serum.

Limitations of the data in this study also deserve comment. First, the number of volunteers studied was small (n = 6), and all volunteers were in good health and had no significant organ dysfunction. Whether the pharmacokinetics and SBAs would have been different in sick or hospitalized elderly patients is uncertain; however, these data should provide better predictions of therapeutic activities of drugs in the elderly than would information obtained from young volunteers. Second, there was considerable variability in the pharmacokinetic parameters studied (Tables 2 and 3) as well as in the SBAs in individual volunteers (data not shown in Table 4). If a larger cohort of volunteers had been studied, there would be greater confidence in the mean or median parameters presented in Tables 2 through 4. Third, only one representative isolate of each bacterial species was used for the measurement of SBA. Although the isolates selected all were proven pathogens from human blood and exhibited MICs and MBCs characteristic for each species, testing of multiple strains of each species would have been preferable. Finally, we did not measure all pharmacokinetic parameters. Analyses of protein binding, renal clearance, and free drug concentrations and measurement of the concentration of the active metabolite of cefotaxime were not done.

Since measurement of SBA takes into consideration in vitro activity, drug pharmacokinetics, and drug pharmacodynamics, we believe our results provide a rational basis for initial dosing of these cephalosporins in the elderly. All had excellent SBAs against the *E. coli* and *K. pneumoniae* strains tested, and for susceptible isolates, all could probably be provided at a lower dose or at a less frequent dosing interval than those usually prescribed (17, 26). Against *S. aureus*, ceftizoxime provided the highest SBA, although it is questionable whether ceftizoxime or other members of this group of antimicrobial agents should be used as primary agents for therapy of *S. aureus* infections. Ceftazidime was the most active agent against *E. aerogenes* and was the only cephalosporin with substantial activity against *P. aeruginosa*; for both microorganisms, significant SBA was present for 8 h after dosing.

The results of this study provide important information concerning the pharmacokinetic and pharamacodynamic properties of expanded-spectrum cephalosporins in the elderly and should help optimize the use of these agents. It would be useful, however, to have additional data from

multidose crossover studies as well as clinical data from hospitalized elderly patients to confirm our observations.

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LITERATURE CITED

1. **Balant, L., P. Dayer, and R. Auckenthaler.** 1985. Clinical pharmacokinetics of the third generation cephalosporins. Clin. Pharmacokinet. **10**:101–143.
2. **Balant, L., P. Dayer, M. Rudhardt, A. F. Allaz, and J. Fabre.** 1980. Cefoperazone: pharmacokinetics in humans with normal and impaired renal function and pharmacokinetics in rats. Clin. Ther. **3**(Special Issue):50–59.
3. **Barriere, S. L., E. Ely, J. E. Kapusnik, and J. G. Gambertoglio.** 1985. Analysis of a new method for assessing activity of combinations of antimicrobials: area under the bactericidal activity curve. J. Antimicrob. Chemother. **16**:49–59.
4. **Barriere, S. L., D. C. Ozasa, and J. Mordenti.** 1985. Assessment of serum bactericidal activity after administration of cefoperazone, cefotaxime, ceftizoxime, and moxalactam to healthy subjects. Antimicrob. Agents Chemother. **28**:55–57.
5. **Cochet, B., J. Belaieff, A. F. Allaz, M. Rudhardt, L. Balant, and J. Fabre.** 1981. Decreased extra-renal clearance of cefoperazone in hepatocellular diseases. Br. J. Clin. Pharmacol. **11**:389–390.
6. **Cockcroft, D. W., and M. H. Gault.** 1976. Prediction of creatinine clearance from serum creatinine. Nephron **16**:31–41.
7. **Coleman, D. L., R. I. Horwitz, and V. T. Andriole.** 1982. Association between serum inhibitory and bactericidal concentrations and therapeutic outcome in bacterial endocarditis. Am. J. Med. **73**:260–267.
8. **Craig, W. A.** 1980. Single-dose pharmacokinetics of cefoperazone following intravenous administration. Clin. Ther. **3**(Special Issue):46–49.
9. **Cutler, R. E., A. D. Blair, E. D. Burgess, and D. Parks.** 1982. Pharmacokinetics of ceftizoxime. J. Antimicrob. Chemother. **10**(Suppl. C):91–97.
10. **Dayer, P., L. Balant, J. Fabre, M. Rudhardt, and A. F. Allaz.** 1981. Renal and extrarenal clearance of cefoperazone in patients with renal failure. Int. J. Clin. Pharmacol. Res. **1**:233–244.
11. **Devine, B. J.** 1974. Gentamicin therapy. Drug Intell. Clin. Pharm. **8**:650–655.
12. **Donne, A.** 1985. JANA: a new iterative polyexperimental curve stripping program. Comput. Method Program Biomed. **20**:269–279.
13. **Drusano, G. L., J. Joshi, A. Forrest, R. Ruxer, H. Standiford, J. Leslie, J. Wade, and S. Schimpff.** 1985. Pharmacokinetics of ceftazidime, alone or in combination with piperacillin or tobramycin, in the sera of cancer patients. Antimicrob. Agents Chemother. **32**:605–607.
14. **Dubois, D., and E. F. Dubois.** 1916. A formula to estimate the approximate surface area if height and weight be known. Arch. Intern. Med. **17**:863–871.
15. **Echols, R., S. Kowalsky, J. Samies, E. McCormick, and M. Fedigan.** 1986. Serum bactericidal activity of cefotaxime, cefoperazone, and ceftizoxime: correlation with pharmacokinetic parameters. Infect. Med. **March**(Suppl.):4–8.
16. **Gibaldi, M., and D. Perrier.** 1987. Pharmacokinetics, 2nd ed., p. 119–128. Marcel Dekker, Inc., New York.
17. **Goodpasture, H. G., E. H. Gerlach, R. N. Jones, and J. D. Peterie.** 1988. Optimal cefotaxime dosing for gram-negative bacteremia: effective trough serum bactericidal titers and drug concentrations 8 and 12 hr after 1- or 2-gm infusions. Diagn. Microbiol. Infect. Dis. **9**:97–103.
18. **Guglielmo, B. J., and L. C. Rodondi.** 1988. Comparison of antibiotic activities by using serum bactericidal activity over time. Antimicrob. Agents Chemother. **32**:1511–1514.
19. **Hayton, W. L., and K. Stoeckel.** 1986. Age-associated changes in ceftriaxone pharmacokinetics. Clin. Pharmacokinet. **11**:76–86.
20. **Heim-Duthoy, K. L., M. P. Bubrick, D. M. Cocchetto, and G. R. Matzke.** 1988. Disposition of ceftazidime in surgical patients with intra-abdominal infection. Antimicrob. Agents Chemother. **32**:1845–1847.
21. **Jonsson, M., and M. Walder.** 1986. Pharmacokinetics of intravenous antibiotic in acutely ill elderly patients. Eur. J. Clin. Microbiol. **5**:629–633.
22. **Klastersky, J.** 1983. The bactericidal activity in serum and its prognostic clinical value. Infection **11**(Suppl. 2):S93–S96.
23. **Lam, Y. W. F., M. H. Doroux, J. G. Gambertoglio, S. L. Barriere, and B. J. Guglielmo.** 1988. Effect of protein binding on serum bactericidal activities of ceftazidime and cefoperazone in healthy volunteers. Antimicrob. Agents Chemother. **32**:298–302.
24. **LeBel, M., G. Barbeau, F. Vallee, and M. G. Bergeron.** 1985. Pharmacokinetics of ceftazidime in elderly volunteers. Antimicrob. Agents Chemother. **28**:713–715.
25. **Leggett, J. E., and W. A. Craig.** 1989. Enhancing effect of serum ultrafiltrate on the activity of cephalosporins against gram-negative bacilli. Antimicrob. Agents Chemother. **33**:35–40.
26. **Ljungberg, B., and I. Nilsson-Ehle.** 1984. Pharmacokinetics of ceftazidime in elderly patients and young volunteers. Scand. J. Infect. Dis. **16**:325–326.
27. **Luderer, S. R., I. H. Patel, J. Durkin, and D. W. Schneck.** 1984. Age and ceftriaxone kinetics. Clin. Pharmacol. Ther. **35**:19–25.
28. **Lüthy, R., J. Blaser, A. Bonetti, H. Simmen, R. Wise, and W. Siegenthaler.** 1981. Comparative muliple-dose pharmacokinetics of cefotaxime, moxalactam, and ceftazidime. Antimicrob. Agents Chemother. **20**:567–575.
29. **McCormick, E. M., R. M. Echols, and T. M. Rosano.** 1984. Liquid chromatographic assay of ceftizoxime in sera of normal and uremic patients. Antimicrob. Agents Chemother. **25**:336–338.
30. **Meyers, B. R., M. N. Mendelson, R. G. Deeter, E. Srulevitch-Chin, M. T. Sarni, and S. Z. Hirschman.** 1987. Pharmacokinetics of cefoperazone in ambulatory elderly volunteers compared with young adults. Antimicrob. Agents Chemother. **31**:925–929.
31. **Muhlberg, W., and D. Platt.** 1982. Cefotaxim. Pharmakokinetik bei geriatrischen Patienten mit Multimorbiditat. Med. Welt. Bd. **33**:551–560.
32. **Naber, K., and D. Adam.** 1980. Pharmakokinetik von cefotaxim bei geriatrischen Patienten. Munch. Med. Wochenschr. **122**: 1651–1654.
33. **Naber, K. G., F. Kees, and N. Grobecker.** 1983. Ceftazidime: pharmacokinetics in young volunteers versus elderly patients and therapeutic efficacy with complicated urinary tract infections. J. Antimicrob. Chemother. **12**(Suppl. A):41–45.
34. **National Committee for Clinical Laboratory Standards.** 1985. Approved standard M7-A. Methods for dilution antimicrobial susceptibility tests for bacteria which grow aerobically. National Committee for Clinical Laboratory Standards, Villanova, Pa.
35. **National Committee for Clinical Laboratory Standards.** 1987. Proposed guideline M21-P. Methodology for the serum bactericidal test. National Committee for Clinical Laboratory Standards, Villanova, Pa.
36. **National Committee for Clinical Laboratory Standards.** 1987. Proposed guideline M26-P. Methods for determining bactericidal activity of antimicrobial agents. National Committee for Clinical Laboratory Standards, Villanova, Pa.
37. **Quintiliani, R., and C. H. Nightingale.** 1982. Comparative pharmacokinetics of ceftizoxime and other third-generation cepholosporins in humans. J. Antimicrob. Chemother. **10**(Suppl. C):99–104.
38. **Quintiliani, R., C. H. Nightingale, and R. Tilton.** 1984. Comparative pharmacokinetics of cefotaxime and ceftizoxime and the role of desacetylcefotaxime in the antibacterial activity of cefotaxime. Diagn. Microbiol. Infect. Dis. **2**(Suppl.):63–70.
39. **Patel, I. H., K. Miller, R. Weinfeld, and J. Spicehandler.** 1981. Multiple intravenous dose pharmacokinetics of ceftriaxone in

man. Chemotherapy 27(Suppl. 1):47–56.
40. **Reller, L. B., and C. W. Stratton.** 1977. Serum dilution test for bactericidal activity. II. Standardization and correlation with antimicrobial assays and susceptibility tests. J. Infect. Dis. **136**:196–204.
41. **SAS Institute Inc.** 1985. SAS/STAT guide for personal computers, version 6. SAS Institute Inc., Cary, N.C.
42. **Schwartz, J. I., L. E. Jauregui, K. A. Bachmann, M. E. Martin, and D. P. Reitberg.** 1988. Multiple-dose pharmacokinetics of intravenously administered cefoperazone and sulbactam when given in combination to infected, seriously ill, elderly patients. Antimicrob. Agents Chemother. **32**:730–735.
43. **Sculier, J. P., and J. Klastersky.** 1984. Significance of serum bactericidal activity in gram-negative bacillary bacteremia in patients with and without granulocytopenia. Am. J. Med. **76**: 429–435.
44. **Signs, S. A., T. M. File, and J. S. Tan.** 1984. High-pressure liquid chromatographic method for analysis of cephalosporins. Antimicrob. Agents Chemother. **26**:652–655.
45. **Standiford, H. C., G. L. Drusano, W. B. MacNamee, B. Tatem, P. A. Ryan, and S. C. Schimpff.** 1982. Comparative pharmacokinetics of moxalactam, cefoperazone, and cefotaxime in normal volunteers. Rev. Infect. Dis. **4**(Suppl.):5585–5594.
46. **Statistical Consultants, Inc.** 1986. PCNONLIN and NONLIN 84: software for the statistical analysis of nonlinear models. Am. Statistician **25**:40–52.
47. **Stratton, C. W., M. P. Weinstein, and L. B. Reller.** 1982. Correlation of serum bactericidal activity with antimicrobial agent level and minimal bactericidal concentration. J. Infect. Dis. **145**:160–168.
48. **Trautmann, K. H., and P. Haefelfinger.** 1981. Determination of cephalosporin Ro 13-9904 in plasma, urine and bile by means of ion-pairing reverse phase chromatography. J. High Resolut. Chromatogr. Commun. **4**:54–59.
49. **Van Laethem, Y., H. Lagast, M. Husson, and J. Klastersky.** 1983. Serum bactericidal activity of cefoperazone and ceftazidime at increasing dosages against Pseudomonas aeruginosa. J. Antimicrob. Chemother. **12**:475–480.
50. **Van Laethem, Y., H. Lagast, and J. Klastersky.** 1983. Serum bactericidal activity of ceftazidime and cefoperazone alone or in combination with amikacin against *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Antimicrob. Agents Chemother. **23**:435–439.
51. **Warns, H., H. Lode, C. M. Harnoss, B. Kemmerich, P. Koeppe, and J. Wagner.** 1983. Multiple dose pharmacokinetics and therapeutic results with ceftazidime. J. Antimicrob. Chemother. **12**(Suppl. A):235–240.
52. **Weinstein, M. P., C. W. Stratton, A. Ackley, H. B. Hawley, P. A. Robinson, B. D. Fisher, D. V. Alcid, D. S. Stephens, and L. B. Reller.** 1985. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. Am. J. Med. **78**:262–268.
53. **Weinstein, M. P., C. W. Stratton, H. B. Hawley, A. Ackley, and L. B. Reller.** 1987. Multicenter collaborative evaluation of a standardized serum bactericidal test as a predictor of therapeutic efficacy in acute and chronic osteomyelitis. Am. J. Med. **83**:218–222.
54. **Wolfson, J. S., and M. N. Swartz.** 1985. Serum bactericidal activity as a monitor of antibiotic therapy. N. Engl. J. Med. **312**:968–975.