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Comparative Pharmacokinetics of Cefamandole, Cephapirin, and Cephalothin in Healthy Subjects and Effect of Repeated Dosing

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Cefamandole nafate, cephapirin, and cephalothin were administered intravenously in crossover fashion to 12 volunteers, in dosages of 2 g every 6 h for 16 doses. Mean peak levels of cefamandole were approximately 50% higher than those of the other agents. The serum concentration curves appeared to decline bi-exponentially, suggesting that a two-compartment model was most applicable for pharmacokinetic analysis; accordingly, the $t_{1/2}$ of cefamandole was significantly longer when the serum peak was omitted from the analysis (0.86 versus 0.73 h, $P < 0.05$). The half-lives of cephalothin and cephapirin, 0.34 and 0.36 h, respectively, were probably underestimates reflecting the inclusion of distribution-phase values in the calculation. Repeated dosing had no effect on the peak serum levels, half-life, serum clearance, or apparent volume of distribution with one exception: peak serum levels of cephapirin were significantly lower after the sixteenth than after the first dose. Marked variations within a given subject were noted in the half-life and apparent volume of distribution of cefamandole in several instances. Renal clearances of cefamandole exhibited saturation kinetics similar to those of penicillin G.

Cefamandole is a new cephalosporin with an extended spectrum against gram-negative bacilli (4). Recently, some aspects of its pharmacology have been reported; these suggest that it produces serum levels slightly higher than those of cephalothin, possesses a half-life similar to that of cephalothin, and displays the kinetics of a one-compartment model (5, 9, 12). The pharmacological behavior of cephapirin, while not extensively studied, appears to be similar to that of cephalothin; however, direct crossover comparisons of the two drugs are lacking (1, 10).

The present investigation was carried out as part of an examination of the comparative phlebitogenic potential of cefamandole, cephapirin, and cephalothin in healthy volunteers (3). The design of the study afforded an opportunity to compare the pharmacokinetics of the three drugs after single and multiple doses, the extent of intra-subject variability in these parameters, and the applicability of a one-compartment model to the kinetic analysis. In addition, the findings emphasize the effect of the serum level of cefamandole on its apparent renal clearance.

MATERIALS AND METHODS

The design of the present study, which was carried out during an investigation of the phlebitogenic potential of these cephalosporins, has been described (3). Briefly, 12 healthy volunteers were given cefamandole nafate, sodium cephapirin, or buffered sodium cephalothin in a dosage of 2 g every 6 h for 4 days; the drugs were administered intravenously over 30 min using an infusion pump. Each subject, with two exceptions, received all three drugs in randomized crossover fashion with a 24-h lapse between courses of therapy. Specimens of blood were obtained at 0.5 (peak), 1.5, 2.5, 4.5, and 6 h after the beginning of the first and last (sixteenth) infusions of each agent. Corresponding urine specimens were collected from 0 to 2 and 2 to 6 h after the onset of the infusion.

Assays for antibiotic content were done by an agar-diffusion bioassay using Trypticase soy agar plates seeded with *Bacillus subtilis* ATCC 6633 (2). Laboratory standard powders, furnished by Eli Lilly and Co. (sodium cephalothin and lithium cefamandole) and Bristol Laboratories (sodium cephapirin), were dissolved in pooled human serum and phosphate-buffered saline for the assay of serum and urine specimens, respectively. Samples containing high concentrations of drug were diluted appropri-

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ately. The assay had an accuracy of ±10% and a sensitivity of 0.3 μg/ml in serum.

The serum protein binding of cefamandole was measured by equilibrium dialysis at an initial antibiotic concentration of 20 μg/ml (2).

Pharmacokinetic analyses. Serum concentrations were plotted on semilogarithmic coordinates, and the first-order elimination rate constants (K) were determined from the slope of the least-squares linear regression line. Because of the apparent biphasic slopes of the curves, K values for cefamandole were determined with and without the 0.5-h value; however, for cephalothin and cephapirin, which were often undetectable in the serum at 4.5 h, the 0.5-h measurement had to be included in all calculations of K. The elimination half-life ($t_{1/2}$) was computed according to the usual equation: $t_{1/2} = \ln 2/K = 0.693/K$. Serum clearance and apparent volume of distribution (AVD) were estimated using the formulas: serum clearance = dose/AUC, and AVD = serum clearance/K, where AUC represents the total area under the serum concentration-time curve, calculated using the trapezoidal rule.

Renal clearance was determined from the usual formula, UV/P, where U and V represent urinary concentration and volume, respectively, and P is the midpoint serum level of drug. For the 0- to 2- and 2- to 6-h urine collections, the values for P at 1 and 4 h were approximated by linear interpolation at appropriate intervals in the individual plots of serum concentration. Measurements of serum and urine creatinine concentration were made by Autoanalyzer.

Statistical analyses were done by the paired t test, using only those values for which both members of the pair were available.

RESULTS

Serum concentration. A semilogarithmic plot of the mean serum levels of each drug at various intervals after the first and sixteenth doses suggested a biphasic curve (Fig. 1 and 2). A similar bi-exponential decline was noted when the values for individual subjects were plotted. The mean and standard error of the peak levels after the first and sixteenth doses were: cefamandole, 147 ± 16 and 157 ± 23 μg/ml; cephapirin, 127 ± 17 and 92 ± 11 μg/ml; and cephalothin, 96 ± 13 and 79 ± 12 μg/ml. The differences between values for the first and last doses were significant for cephapirin ($P < 0.01$). Levels of cefamandole were significantly higher than those of cephalothin after the first dose and higher than those of both cephalothin and cephapirin after the sixteenth dose ($P < 0.05$ in each instance). In addition to the marked inter-individual variations that are evident from the standard error, differences between values for the first and last doses within the same subject were sometimes striking.

Serum half-life. There were no significant changes in half-life values between the first and last doses for any of the agents (Table 1). When the data for each drug were pooled, the overall half-life values (mean ± standard deviation) were: cefamandole, 0.86 ± 0.25 h; cephapirin, 0.36 ± 0.08 h; and cephalothin, 0.34 ± 0.06 h. Inclusion of the levels at 0.5 h in the calculation for cefamandole shortened the overall half-life significantly (0.86 versus 0.73 h, $P < 0.05$). The resultant value was still substantially longer than the half-life of either cephalothin or cephapirin.

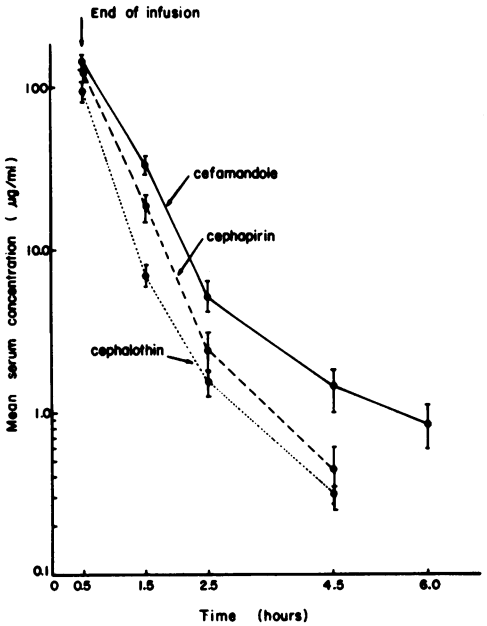

FIG. 1. *Semilogarithmic plot of mean serum concentrations of antibiotic at various intervals after the first dose of drug. Vertical bars represent standard error.*

Intra-subject variations in the half-life of cephalothin or cephapirin were small (Table 1). In contrast, differences approaching twofold were noted in subjects 3 and 4 for cefamandole.

Serum clearance, renal clearance, and AVD of cefamandole. There was no difference between values for the first and sixteenth doses in terms of serum clearance, AVD, or renal clearance of cefamandole (Table 2). These parameters could not reliably be measured for cephalothin and cephapirin because the rapid elimination of these drugs afforded only a limited number of serum levels. Overall measurements (mean ± standard deviation) of the serum clearance and AVD of cefamandole were 230 ± 99 ml/min per 1.73 m^2 and 17.9 ± 8.4 liters, respectively. The AVD ranged from 10 to 67% of body weight, with most values falling between 20 and 30%. There was no significant correla-

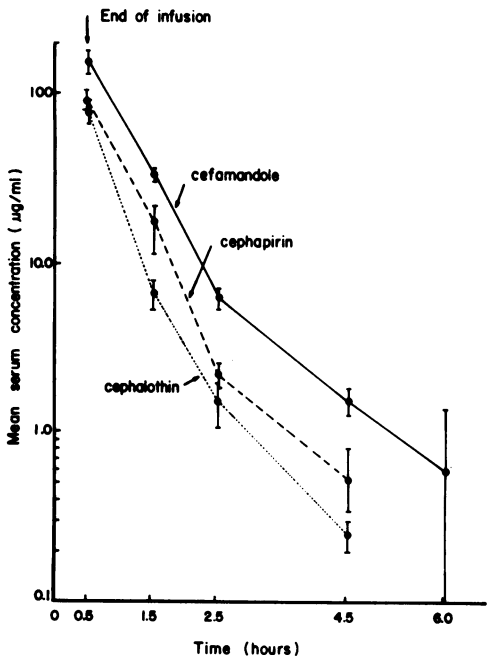

FIG. 2. *Semilogarithmic plot of mean serum concentrations of antibiotic at various intervals after the last dose of drug. Vertical bars represent standard error.*

TABLE 1. *Serum half-life (hours) after first and sixteenth doses of three cephalosporins*[a]

Subject	Cefamandole		Cephapirin		Cephalothin	
	1st dose	16th dose	1st dose	16th dose	1st dose	16th dose
1	0.72	0.84	0.37	0.35	0.33	0.39
2	1.0	0.81	0.40		0.28	0.28
3	1.8	0.92	0.35	0.29	0.34	
4	0.49	0.82	0.27		0.29	
5	0.79	0.78		0.30	0.26	0.26
6	1.1	0.71	0.33	0.37	0.47	0.37
7	0.79	0.74	0.37	0.41		0.36
8	0.68	0.88	0.29		0.34	0.38
9	0.89	0.80	0.23	0.35	0.34	0.35
10	0.89		0.33	0.36		
11			0.63	0.40	0.38	
12	0.72	0.89		0.40		0.44
Mean	0.90	0.82	0.36	0.36	0.34	0.35
SD[b]	0.34	0.07	0.11	0.04	0.06	0.06

[a] Values for cefamandole were computed from serum levels at 1.5, 2.5, 4.5, and 6 h; for cephalothin and cephapirin, data for 0.5, 1.5, 2.5, and (where detectable) 4.5 h were used.

[b] SD, Standard deviation.

tion between AVD and body weight. Intra-subject variations in serum clearance and in AVD were striking in a number of instances (Table 2).

When the renal clearances of cefamandole were plotted against midpoint serum concentrations (P), the data fell into two groups: those obtained at 0 to 2 h (serum levels of 48 to 128 μg/ml) and those obtained at 2 to 6 h (serum levels of ≤5 μg/ml; Fig. 3). With two exceptions, clearance values at the higher serum concentrations were close to 100 ml/min per 1.73 m², whereas those at lower concentrations ranged from 220 to 670 ml/min per 1.73 m².

TABLE 2. *Serum clearance and AVD after the first and sixteenth doses of cefamandole*

Subject	Serum clearance (ml/min per 1.73 m²)		AVD (liters)	
	1st dose	16th dose	1st dose	16th dose
1	182	193	11.4	14.1
2	329	389	30.6	29.3
3	250	134	40.1	11.0
4	531	117	24.1	8.9
5	197	285	13.1	18.7
6	260	166	21.7	9.0
7	266	268	20.8	19.7
8	196	276	14.4	26.3
9	192	167	17.6	13.7
10	120		9.2	
12	132	181	7.5	15.3
Mean	241	218	19.1	16.6
SD[a]	114	84	9.8	6.9

[a] SD, Standard deviation.

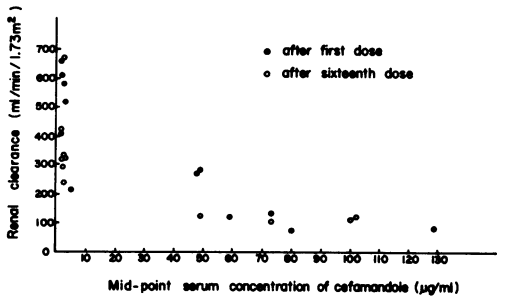

FIG. 3. *Relation between the renal clearance of cefamandole, as determined from the formula UV/P, and the midpoint serum concentration of antibiotic.*

Serum protein binding. The mean value in 13 chambers was 67% (standard deviation, 2%), with a range of 56 to 78%.

DISCUSSION

The results of this study indicate that cefamandole produces higher levels of drug in the serum than those found after an equivalent dose of cephalothin or cephapirin. Its degree of serum protein binding is similar to that of cephalothin (5) and slightly higher than the 44 to 54% reported for cephapirin (7). Higher levels of cefamandole than of cephalothin have been re-

ported by Fong et al. (5), and indirect comparisons of the serum levels of cephalothin and cephapirin are in agreement with the findings in the present study (1, 10). Because serum was not obtained during the infusion phase in the present study, the pharmacokinetic analysis slightly underestimates the AUC value and therefore overestimates that of serum clearance and AVD. Nevertheless, the serum clearances of cefamandole are in excellent agreement with those reported by Fong et al. (5). Values previously reported for the AVD of cefamandole include 17.1 liters (24% of body weight) and 12.8 liters/1.73 m^2 (5, 9), which are similar to our results obtained in the postdistribution phase.

The pharmacokinetic analysis is complicated somewhat by the biotransformation undergone by all threee agents. Cefamandole nafate is hydrolyzed in vivo to the active drug, cefamandole. Because of the rapidity of this process ($t_{1/2}$ about 13 min; J. S. Wold, R. R. Joost, and J. M. Indelicato, Prog. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 15th, Washington, D.C., Abstr. 82, 1975), it is unlikely that it appreciably affected the pharmacokinetic measurements. Cefamandole itself appears not to be metabolized as indicated by the extent of its urinary recovery (9) and by the similarity of its renal and serum clearance rates (5). Both cephalothin and cephapirin are metabolized to the less active *o*-desacetyl derivative, which comprises 33 and 41%, respectively, of the antibiotic found in the urine (10). Data from our own laboratory for cephalothin (unpublished data) and from Bristol Laboratories for both drugs (B. E. Cabana, unpublished data) indicate that in healthy individuals, levels of the desacetyl derivatives are only 5 to 15% of the concentrations of the parent substance in serum. Since the metabolite is one-fifth as active against the test organism (*B. subtilis*) as is cephalothin (8) or cephapirin (Bristol Laboratories, unpublished data), its presence appears unlikely to have interfered with the assay of the parent compound.

The rapid elimination of the cephalosporins would suggest that their peak serum levels and other pharmacokinetic characteristics should not be affected by repeated dosing (10). In one study of cefazolin, however, a reduction in the half-life was noted after multiple injections (13). In the present study, repeated administration did not influence the peak serum levels or half-life of these cephalosporins, or the serum clearance or AVD of cefamandole. One unexpected exception was cephapirin, for which peak serum levels were slightly, but significantly, lower after the sixteenth than after the first dose. We have no explanation for this observation; moreover, no such difference was apparent at the 1.5-h (18.6 versus 17.8 μg/ml) and 2.5-h (2.4 versus 2.2 μg/ml) intervals after the first and last doses of cephapirin. In any event, the extent of the decrease appears unlikely to be of clinical importance.

Except for the peak serum levels of cephapirin, there was no significant overall change in any of the pharmacokinetic measurements with repeated dosing; thus, it was of interest to examine the extent of variations in these parameters between the first and the last doses in the same individual. The serum half-lives of cephalothin and cephapirin were quite consistent for a given subject; in contrast, the half-life of cefamandole showed marked variations (twofold) in two recipients. The same individuals exhibited similar discrepancies in the serum clearance of this agent, and four volunteers displayed striking changes in the AVD of cefamandole.

Many authors have used a one-compartment model to analyze the pharmacokinetics of cephalosporins. Nightingale et al. have emphasized the problems of this approach which, by including the early, short-lived "distribution" phase, results in an artificially short serum half-life (10). They have noted that the kinetics of most cephalosporins best fit a two-compartment model. Figures 1 and 2 support the notion that the serum levels of these drugs exhibit a biphasic decline. For cefamandole, the distributive phase, during which serum levels declined very rapidly, lasted about 2 h; thereafter, levels decreased more slowly. Accordingly, exclusion of the 0.5-h serum level from the calculation resulted in a significant increase in the half-life (0.86 versus 0.73 h, $P < 0.05$), approximating more closely the β-phase half-life of the drug. Recently, Fong et al. reported that the elimination kinetics of cefamandole appeared to fit a one-compartment model (5); however, they examined the kinetics after infusion to steady state in one group (an approach that may have impaired the ability to discern the two-compartment characteristics of the drug [6]) and excluded serum levels obtained 30 to 45 min postinfusion in the other (5). The half-life of cefamandole in that study (0.56 h) was substantially shorter than our value; one possible explanation is that the higher dose of drug used in the present investigation saturated the renal clearance mechanisms, resulting in a longer $t_{1/2}$. In addition, inter-subject variations may have played a role in the difference.

It should be noted that the half-lives of cephalothin and cephapirin measured in this study were largely based upon the 0.5-, 1.5-, and 2.5-h serum levels and therefore probably include an

appreciable contribution of the distributive phase. A more accurate measurement of the elimination rate of these rapidly excreted agents might better be made after infusion to equilibrium. Although the importance of these distinctions might not appear great, their influence on measurements of AVD and absorption and elimination rate constants is substantial (10), especially since the discrepancy between distributional and elimination-phase half-lives for cephalosporins is typically about fivefold.

A marked effect of serum level on the apparent clearance rate of cefamandole was noted (Fig. 3). This result was not surprising and simply reflects the saturability of the transport pump for organic anions of the proximal renal tubule (11). Although the lack of data in the middle range of serum concentrations precludes precise definition of the T_m of cefamandole, the shape of the curve suggests a value similar to that for penicillin G (11). This phenomenon probably also contributes to the divergent results reported by various investigators for the renal clearance of beta-lactam antibiotics.

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