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Disposition of Cefmetazole in Healthy Volunteers and Patients with Impaired Renal Function

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The disposition of cefmetazole was studied in 25 subjects with various degrees of renal function after a 1,000-mg, constant-rate, 30-min intravenous infusion of cefmetazole sodium. In six subjects with creatinine clearance (CL_{CR}) of >90 ml/min per 1.73 m^2 (group 1), the terminal elimination half-life ($t_{1/2\beta}$) was 1.31 ± 0.54 h (mean ± standard deviation), cefmetazole total body clearance (CL_P) was 132.8 ± 25.1 ml/min per 1.73 m^2, and volume of distribution at steady state was 0.165 ± 0.025 liter/kg. The fraction of dose excreted unchanged in the urine was 84.0% ± 26.1%. Subjects with CL_{CR}s of 40 to 69 (group 2, n = 6) and 10 to 39 (group 3, n = 6) ml/min per 1.73 m^2 demonstrated prolongation of the $t_{1/2\beta}$ (3.62 ± 1.06 and 5.93 ± 1.81 h, respectively) and significant reductions in cefmetazole CL_P (52.8 ± 14.3 and 30.2 ± 10.2 ml/min per 1.73 m^2, respectively), compared with group 1. In seven subjects on chronic hemodialysis (group 4) studied during an interdialytic period, the cefmetazole $t_{1/2\beta}$ was increased to 24.10 ± 8.12 h and the CL_P was reduced to 6.8 ± 2.1 ml/min per 1.73 m^2. Cefmetazole CL_P correlated positively with CL_{CR} (r = 0.951, $P < 0.001$): $CL_P = (1.181 \cdot CL_{CR}) - 0.287$. The disposition of cefmetazole was also assessed in six group 4 subjects during an intradialytic period. The $t_{1/2\beta}$ during hemodialysis (2.09 ± 0.69 h) was significantly shorter than that observed during the interdialytic period. The hemodialysis clearance of cefmetazole was 86.1 ± 20.1 ml/min, and the fraction of cefmetazole removed during hemodialysis was 59.8% ± 5.9%. It is recommended that patients with renal insufficiency receive standard doses of cefmetazole at extended intervals and patients on maintenance hemodialysis receive standard doses after hemodialysis.

Cefmetazole sodium is an investigational parenteral cephamycin antibiotic possessing activity against a broad spectrum of both gram-positive and gram-negative aerobic and anaerobic bacteria (3, 6, 11, 13). The MIC for 90% of strains of clinically important pathogens, such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis*, *Haemophilus influenzae*, and *Neisseria* spp., ranges between 0.012 and 4 μg/ml (6). Clinical studies in humans have demonstrated efficacy in the treatment of various infections (15), including pneumonia (L. A. Von Behren, T. E. King, R. P. Tewari, and S. Rabinovich, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 850, 1987) and skin and soft tissue infections (E. Frank, S. Phillips, and T. Gupta, 27th ICAAC, abstr. no. 98, 1987).

Single-dose intravenous pharmacokinetic studies in healthy human volunteers have reported mean peak concentration of 290 μg/ml in plasma after a 2-g bolus (7), mean terminal elimination half-lives ($t_{1/2\beta}$s) ranging from approximately 0.8 to 1.8 h (7, 12, 14), and mean cumulative urinary recoveries of intact drug of 71% within 24 h of drug administration (7). In patients with creatinine clearances (CL_{CR}s) below 10 ml/min, the $t_{1/2\beta}$ of cefmetazole has been reported to be prolonged to approximately 15 h (12). The group, however, included nonhemodialysis and hemodialysis patients evaluated during an interdialytic period. The effect of hemodialysis on cefmetazole disposition has not yet been reported.

This study was designed to characterize the disposition of cefmetazole after the administration of a single intravenous dose in subjects with various degrees of renal function and to assess the effect of hemodialysis on the disposition of cefmetazole.

MATERIALS AND METHODS

Subjects and study design. Twenty-five subjects between the ages of 18 and 75 years participated in the study after granting written informed consent. Each participant underwent a medical history, physical examination, laboratory evaluation, chest X-ray, and electrocardiogram prior to study participation. Participants were divided into groups based on measured ambulatory 24-h CL_{CR} obtained prior to study participation. Groups 1, 2, and 3 had CL_{CR}s greater than 90, 40 to 69, and 10 to 39 ml/min per 1.73 m^2, respectively. Group 4 consisted of subjects with CL_{CR}s less than 10 ml/min per 1.73 m^2 maintained on chronic hemodialysis. Concurrent drug therapy was permitted for subjects in groups 2, 3, and 4. These included drugs for the treatment of hypertension, diabetes, and hyperparathyroidism. All such concurrent therapy was continued unchanged for 2 weeks prior to the study and during the course of the investigation.

Subjects in groups 1, 2, and 3 received a single 1,000-mg dose of cefmetazole sodium (lot 23,234; The Upjohn Co., Kalamazoo, Mich.) as a constant 30-min intravenous infusion via a volumetric infusion pump (Travenol Flowgard-8000; Baxter Travenol, Deerfield, Ill.). Subjects in group 4 received two 1,000-mg doses of cefmetazole sodium separated by 2 to 4 weeks. One dose was administered prior to hemodialysis, and the other was administered during an

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interdialytic period. The order of these administrations was randomly assigned.

All participants were admitted to the Clinical Research Unit 12 h prior to drug administration. Ten hours prior to drug administration, a standard light snack was served, after which each subject fasted until 4 hours after the end of the cefmetazole infusion.

Sample collection. In groups 1, 2, and 3, blood samples were obtained immediately before and 0.167, 0.33, 0.5 (end of infusion), 0.67, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 h after the start of the infusion. From the group 4 subjects evaluated during the interdialytic study phase, blood samples were obtained immediately before and 0.167, 0.33, 0.5 (end of infusion), 0.67, 1, 2, 3, 6, 9, 12, 14, 16, 18, 24, 30, 36, and 48 h (predialysis) after the start of the infusion. On the hemodialysis dosing day, blood samples were drawn immediately before and at 0.167, 0.33, 0.5 (end of infusion), 0.67, and 1 h after initiation of the infusion. At this time, subjects underwent regularly scheduled hemodialysis treatments for a duration of 3 h. Paired arterial (predialysis filter) and venous (postdialysis filter) blood samples were obtained at 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 h after the start of hemodialysis. Additional venous blood samples were obtained at 0.167, 0.5, 0.75, 1, 1.5, 2, 4, 8, 10, 12, 14, 20, 26, 32, and 44 h after the termination of hemodialysis.

Blood specimens were drawn into heparinized tubes from the contralateral arm and immediately placed on ice. Plasma was harvested in precooled (4°C) centrifuge tubes within 30 min of blood collection. The plasma was saved in glass scintillation vials and frozen at −20°C until analysis.

During the hemodialysis procedure, total dialysate effluent was collected over 30-min intervals. The volume of each interval collection was measured, and a sample was saved and frozen at −20°C until analysis.

When possible, urine was collected before the dose and during the following intervals after the start of cefmetazole administration: 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h. During each collection period, the urine flask was stored at 4°C. Urine volumes were quantitated, and a sample was saved and frozen at −20°C until analysis.

Analytic procedures. The concentrations of cefmetazole in plasma and urine samples were determined by a minor modification of a semiautomated high-performance liquid chromatographic method (2). This method was precise and accurate to 2 μg of cefmetazole per ml in plasma and 15 μg of cefmetazole per ml in urine. The intra- and interassay coefficients of variation were less than 15% in plasma at concentrations between 7.8 and 251.2 μg/ml and less than 10% in urine over a range of 60 to 1,000 μg/ml. Drug analysis of cefmetazole in dialysate was performed using a reverse-phase liquid chromatographic method for cefmetazole in solutions, with an intraday coefficient of variation of less than 3% over a concentration range of 10 to 200 μg/ml (data on file, The Upjohn Co.).

Data analysis. The maximum concentration in plasma (C_{max}) was determined from the observed plasma concentration-versus-time data. The cefmetazole plasma concentration-versus-time data were analyzed by using the equations $C = Be^{-\beta t}$ and $C = Ae^{-\alpha t} + Be^{-\beta t}$, where C is the concentration in plasma at time t; A and B are the y intercepts; and α and β are the disposition rate constants obtained from the first and second linear phases, respectively, of the plot of log cefmetazole concentration in plasma versus time. Standard curve-stripping procedures were used to obtain initial estimates, and nonlinear regression analysis (10) was used to obtain final estimates of A, B, α, and β. The central compartment volume of distribution, volume of distribution at steady state (V_{ss}), distribution rate constants k_{12} and k_{21}, and overall elimination rate constant k_{10} were derived from those estimates by using standard techniques (4). The effects of weighting functions 1, $1/y$, and $1/y^2$ on model parameters, where y is the measured concentration of cefmetazole in plasma, were evaluated. The optimal exponential function and optimal compartmental model were determined on the basis of visual inspection, minimization of the residual sum of squares, and Akaike criteria (1). The coefficients of the optimal equation were corrected to values reflecting a single intravenous bolus dose (4).

The area under the plasma concentration-versus-time curve from zero hour to the last measurable sampling time (AUC_{0-t}) was calculated by linear trapezoidal estimation. The AUC from zero hour to infinity ($AUC_{0-\infty}$) was estimated by using the equation $AUC_{0-\infty} = AUC_{0-t} + C_P/\beta$, where C_P represents the last measured concentration in plasma and β is the rate constant of the terminal disposition phase. The total body clearance (CL_P) of cefmetazole was determined by using standard procedures (CL_P = dose/$AUC_{0-\infty}$). The renal clearance (CL_R) of cefmetazole was calculated by using the equation $CL_R = X_u^{1-2}/AUC_{t1-t2}$, where X_u^{1-2} is the amount of cefmetazole recovered in the urine during the urine collection interval from time t_1 to time t_2 and AUC_{t1-t2} is the AUC during the same time interval. For each subject, the CL_R was averaged over the number of urine collection intervals. The nonrenal clearance (CL_{NR}) of cefmetazole was calculated as $CL_{NR} = CL_P - CL_R$.

The alpha-phase half-life ($t_{1/2\alpha}$) and $t_{1/2\beta}$ were calculated by the equations $t_{1/2\alpha} = 0.693/\alpha$ and $t_{1/2\beta} = 0.693/\beta$, respectively.

The hemodialysis plasma clearance (CL_{HD}) of cefmetazole was calculated by using the equation $CL_{HD} = (V_D \cdot C_D)/AUC_{0-t}$, where V_D is the dialysate volume, C_D is the dialysate cefmetazole concentration, and AUC_{0-t} is the AUC over the dialysis time interval. For each patient, CL_{HD} was averaged over the multiple data collected.

The fraction of cefmetazole body burden cleared during hemodialysis (f) was estimated as $f = CL_{HD} \cdot AUC_{HD}/[(CL_{HD} + CL_P) \cdot AUC_{HD} + (CL_P \cdot AUC_{ED-\infty})]$, where AUC_{HD} and $AUC_{ED-\infty}$ are the areas under the predialysis filter plasma concentration-versus-time curve during hemodialysis and from the end of dialysis to infinity, respectively (8).

Statistical analysis. Differences in pharmacokinetic parameters between the four groups were evaluated by analysis of variance, using the Newman-Keuls post hoc test for significance. The correlation between CL_{CR} and various pharmacokinetic parameters was assessed by orthogonal regression analysis. Significance was assessed at $P = 0.05$.

RESULTS

The demographic and clinical characteristics of the 25 study participants are summarized in Table 1. There were no significant differences in age, sex or race distribution, weight, or height among the four groups.

The mean cefmetazole plasma concentration-versus-time data for the four groups are illustrated in Fig. 1. Concentrations in plasma declined in a biexponential manner in 24 of the 25 subjects from peak concentrations achieved at the end of the infusion and monoexponentially in 1 subject.

The one- and two-compartment models were fit to cefmetazole plasma concentration-versus-time data by using the $1/y$ weighting function. Pharmacokinetic parameters for

TABLE 1. Subject demographic characteristics[a]

Group	No. of males/females	Age (yr)	Wt (kg)	Ht (cm)	CL_{CR} (ml/min per 1.73 m^2)
1	4/2	35.8 ± 18.0	73.5 ± 19.5	176.4 ± 10.9	108.6 ± 15.7[b]
2	6/0	43.0 ± 20.3	77.6 ± 11.3	178.2 ± 7.4	59.0 ± 8.4[c]
3	5/1	44.3 ± 17.8	72.2 ± 15.7	177.6 ± 6.0	22.4 ± 8.3
4	3/4	44.3 ± 9.9	70.4 ± 15.3	173.4 ± 9.2	<10, Anuric

[a] Data are presented as means ± standard deviations.
[b] $P < 0.05$, Group 1 versus groups 2 and 3.
[c] $P < 0.05$, Group 2 versus group 3.

the four groups are summarized in Table 2. Mean C_{max}s of cefmetazole did not differ between groups, although a significant correlation with CL_{CR} was demonstrated [$C_{max} = (-0.228 \cdot CL_{CR}) + 105.9$, $r = -0.498$]. The $t_{1/2\beta}$s were significantly longer for groups 2, 3, and 4 than for group 1. The cefmetazole CL_P declined from 132.8 ± 25.1 ml/min per 1.73 m^2 in group 1 to 52.8 ± 14.3, 30.2 ± 10.2, and 6.8 ± 2.1 ml/min per 1.73 m^2 in groups 2, 3, and 4, respectively. Groups 2 and 3 had significantly lower CL_Rs than group 1. The V_{ss}s and nonrenal clearances among the four treatment groups were not significantly different. Mean cumulative urinary recoveries of cefmetazole within 48 h after drug administration for groups 1, 2, and 3 were 84.0% ± 26.2%, 78.4% ± 9.1%, and 60.5% ± 13.7%, respectively.

Cefmetazole CL_P was positively correlated with CL_{CR} (Fig. 2). Both β and CL_R were also significantly correlated with CL_{CR} ($P < 0.001$): $\beta = (0.0048 \cdot CL_{CR}) + 0.0063$ ($r = 0.924$), and $CL_R = (1.027 \cdot CL_{CR}) - 5.800$ ($r = 0.917$).

The cefmetazole predialysis filter, postdialysis filter, and dialysate concentration-versus-time curves during hemodialysis are depicted in Fig. 3. The pharmacokinetic parameters for cefmetazole during hemodialysis are summarized in Table 3. The cefmetazole CL_{HD} was increased approximately 13-fold over the baseline CL_P and represented 34.0% ± 4.5% and 38.2% ± 5.7% of the urea and creatinine hemodialysis clearances, respectively. The fraction of cefmetazole body burden removed during dialysis was 59.8% ± 5.9%. A rebound in cefmetazole concentration in plasma of 3.3 ± 2.4 μg/ml was observed at 0.9 ± 0.4 h following cessation of hemodialysis, representing an increase of 17.9% ± 16.3% from the concentration in plasma measured at the end of hemodialysis. The cefmetazole concentration in plasma then declined monoexponentially, with a $t_{1/2\beta}$ of 29.4 ± 14.6 h.

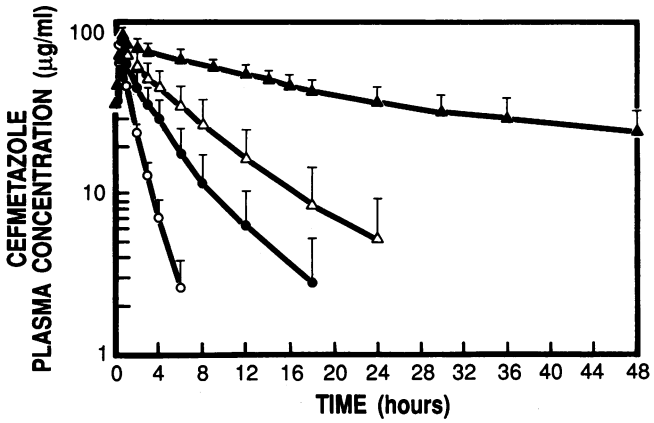

FIG. 1. Cefmetazole plasma concentration-versus-time profiles (mean ± standard deviation) for groups 1 (○), 2 (●), 3 (△), and 4 (interdialytic phase) (▲) following a 1,000-mg, 30-min, constant-rate intravenous infusion.

Adverse events reported during the course of this study which were probably related to cefmetazole sodium administration consisted of six complaints of diarrhea. All the subjects recovered with no sequelae. All abnormal laboratory tests (i.e., mild partial thromboplastin time elevation [$n = 1$], eosinophilia [$n = 1$], drop in hemoglobin [$n = 1$], and conversion of direct Coombs test to positive [$n = 1$]) returned to baseline on follow-up examination.

DISCUSSION

This study demonstrated that the disposition of cefmetazole in subjects with decreased renal function is significantly altered compared with that in subjects with normal renal function. The $t_{1/2\beta}$ and $AUC_{0-\infty}$ increased while the β, CL_P, CL_R, and cumulative urinary recovery of cefmetazole declined as renal function decreased. A significant relationship between CL_P and CL_R was demonstrated. Cefmetazole C_{max}, V_{ss}, and volume of distribution in the central compartment, however, were not altered in the presence of renal insufficiency.

Ohkawa et al. (12) evaluated the pharmacokinetics of cefmetazole in 21 subjects with normal (CL_{CR}, >90 ml/min per 1.73 m^2) and decreased (CL_{CR}, 60 to 90, 30 to 59, and 10 to 29 ml/min per 1.73 m^2) renal function. As in the present study, these investigators observed an unchanged V_{ss}, a decreased CL_P, and an increased $t_{1/2\beta}$ with declining renal function. The CL_P and $t_{1/2\beta}$ reported by the same authors for normal subjects were only slightly different from those of our study; however, the CL_P and $t_{1/2\beta}$ for subjects with CL_{CR}s of <10 ml/min per 1.73 m^2 were significantly different (14.0 ± 6.2 versus 6.8 ± 2.1 ml/min per 1.73 m^2 and 14.98 ± 4.71 versus 24.10 ± 8.12 h, respectively). These differences may be a reflection of the shorter sampling time employed (only 6 h postdose), the use of different assay techniques (microbiological versus high-performance liquid chromatography), or the variability in the patient populations. Furthermore, a one-compartment model was used by Ohkawa et al. (12) to fit the four postdose datum points, whereas our study utilized a two-compartment open model which provided a better fit of the plasma concentration-versus-time data for 24 of 25 subjects. Other differences include the measurement of a greater urinary recovery of intact drug in normal subjects (84%) than the previously reported mean of 69 to 71% (7, 12).

Levy suggested that drug removal during hemodialysis may be considered significant when CL_{HD} is more than 30% greater than CL_P (9). However, Lee and Marbury cautioned that when an indirect index for drug removal is used, the extent of rebound of concentration in plasma after termination of hemodialysis must also be evaluated (8). In this study, a significant enhancement in the CL_{HD} and a slight rebound in cefmetazole concentration in plasma following

TABLE 2. Summary of pharmacokinetic parameters for cefmetazole[a]

Group (n)	C_{max} (μg/ml)	V_1 (liter/kg)	V_{ss} (liter/kg)	$AUC_{0-\infty}$ (μg · h/ml)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	CL_P (ml/min per 1.73 m²)	CL_R (ml/min per 1.73 m²)	CL_{NR} (ml/min per 1.73 m²)	f_e (%)
1 (6)	85.9 ± 11.9	0.094 ± 0.058	0.165 ± 0.025	135.2 ± 17.1	0.25 ± 0.23	1.31 ± 0.54[b]	132.8 ± 25.1[b]	109.0 ± 24.2[c]	27.2 ± 32.7	84.0 ± 26.1
2 (6)	88.5 ± 15.4	0.114 ± 0.023	0.187 ± 0.033	353.2 ± 99.0	0.38 ± 0.28	3.62 ± 1.06	52.8 ± 14.3[d]	42.7 ± 15.2[d]	10.0 ± 5.6	78.4 ± 9.1
3 (6)	97.7 ± 19.8	0.130 ± 0.055	0.175 ± 0.033	642.9 ± 230.2	0.86 ± 1.30	5.93 ± 1.81	30.2 ± 10.2	19.6 ± 9.4	10.6 ± 4.1	60.5 ± 13.7
4[e] (7)	107.7 ± 15.5	0.097 ± 0.037	0.181 ± 0.027	3,436.6 ± 1,634.3[f]	0.24 ± 0.18	24.10 ± 8.12	6.8 ± 2.1[f]	1.18[g]	6.6 ± 2.4	16.4[g]

[a] Data are presented as means ± standard deviations. V_1, Volume of distribution in the central compartment; CL_{NR}, nonrenal clearance; f_e, cumulative urinary recovery. Other abbreviations are defined in the text.
[b] $P < 0.05$, Group 1 versus groups 2, 3, and 4.
[c] $P < 0.05$, Group 1 versus groups 2 and 3.
[d] $P < 0.05$, Group 2 versus group 3.
[e] Interdialytic dose.
[f] $P < 0.05$, Group 4 versus groups 1, 2, and 3.
[g] One subject had residual renal function.

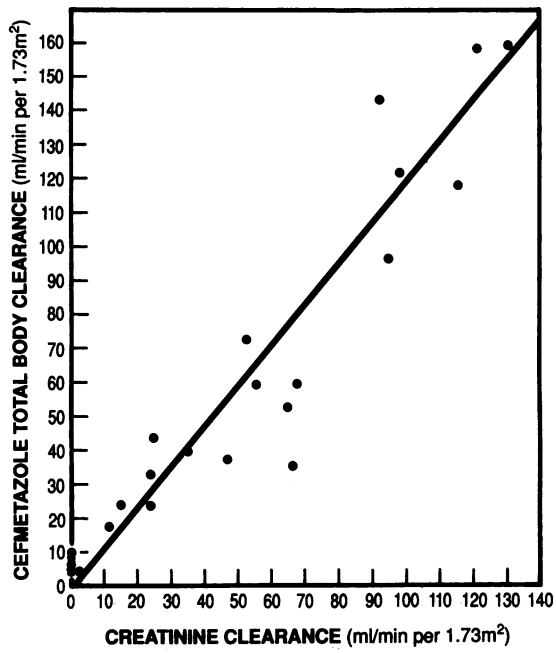

FIG. 2. Correlation of cefmetazole CL_P and CL_{CR}; $CL_P = (1.181 \cdot CL_{CR}) - 0.287$ ($n = 25$, $r = 0.951$, $P < 0.001$).

the cessation of hemodialysis were observed. Therefore, for patients receiving maintenance hemodialysis, scheduling the administration of a standard dose of cefmetazole after hemodialysis is suggested to maintain bactericidal concentrations in plasma.

Modification of cefmetazole sodium dosage regimens for patients with renal impairment is suggested, since accumu-

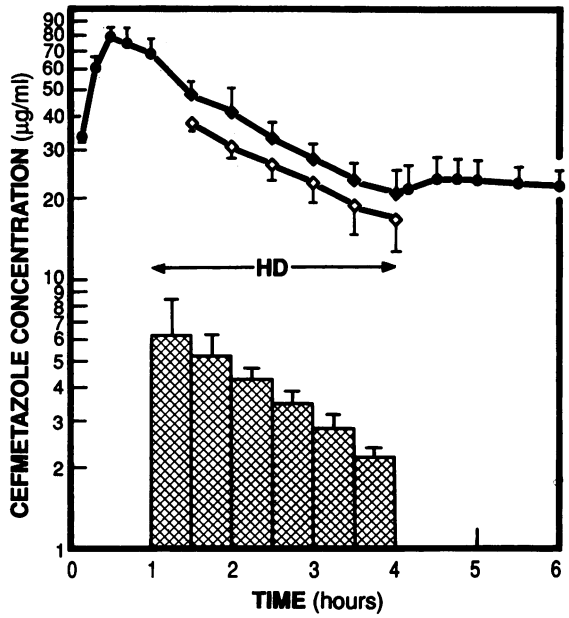

FIG. 3. Cefmetazole interdialytic (●), predialysis filter (◆), and postdialysis filter (◇) plasma concentration-versus-time profiles (mean ± standard deviation) for group 4 ($n = 6$) following a 1,000-mg, 30-min, constant-rate intravenous infusion prior to hemodialysis (HD). Concentrations in dialysate (mean ± standard deviation) are represented by crosshatched bars.

TABLE 3. Hemodialysis procedure characteristics and intra- and postdialysis pharmacokinetic parameters for cefmetazole[a]

Subject no.[b]	Travenol dialyzer filter[c]	Q_D (ml/min)	Q_B (ml/min)	Q_P (ml/min)	$t_{1/2}$ (h)		CL_{HD} (ml/min)	f (%)	Maximum rebound post-HD (μg/ml)	T_{max} for rebound (h)	Rebound change in C_P (%)
					On HD	Off HD					
19	CA210	774	300	172	1.74	10.16	70.0	65.7	5.4	0.9	23.1
21	CA210	792	400	316	1.61	27.34	77.1	58.8	2.7	0.8	14.4
22	CA210	763	400	286	1.83	29.59	89.8	67.3	2.3	0.5	11.7
23	CA170-Tandem	731	500	369	1.52	54.68	118.9	59.8	6.9	1.6	48.1
24	CA170	783	400	255	2.56	22.62	64.1	54.8	2.0	0.8	7.6
25	CA210	757	450	317	3.28	32.03	96.4	52.2	0.6	1.0	2.7
Mean ± SD		767 ± 22	408 ± 66	286 ± 67	2.09 ± 0.69	29.40 ± 14.60	86.1 ± 20.1	59.8 ± 5.9	3.3 ± 2.4	0.9 ± 0.4	17.9 ± 16.3

[a] Q_D, Dialysate flow rate; Q_B, blood pump flow rate; Q_P, average plasma flow rate [$Q_B \cdot (1 - \text{hematocrit})$]; $t_{1/2}$ on HD (hemodialysis), $t_{1/2}$ during intradialytic period; $t_{1/2}$ off HD, $t_{1/2\beta}$ during postdialytic period; f, fraction of cefmetazole cleared during hemodialysis; T_{max}, time to maximum; C_P, concentration in plasma.
[b] Subject 20 was dropped prior to the hemodialysis dosing period due to low hemoglobin.
[c] Travenol SPS 450 dialysis system for all dialysis studies and first-use filter utilized.

lation of the drug is likely to occur with repeated administration. Since the V_{ss} of cefmetazole does not vary with renal function, the dose of cefmetazole sodium may not need to be changed from that utilized for patients with normal renal function. However, due to the decreased CL_P and increased $t_{1/2\beta}$, the dosing interval should be increased to avoid excessive drug accumulation. The proposed dosing interval for patients with normal renal function is 8 h. Using the equation which describes the relationship between CL_P and CL_{CR}, the suggested dosing interval for patients with CL_{CR}s of 51 to 90, 31 to 50, and 10 to 30 ml/min and on maintenance hemodialysis would be 12, 18, 24, and 48 (dose administered after hemodialysis) h, respectively.

Cefmetazole possesses a broad spectrum of activity against a variety of gram-positive and gram-negative bacteria. Utilizing the suggested dosage adjustments, administration of a 2-g dose of cefmetazole provides predicted minimum cefmetazole concentrations in plasma greater than 4 μg/ml, which should inhibit most clinically relevant pathogens. However, it has been noted by Graves (5) that single-dose studies may fail to predict steady-state kinetics; therefore, multiple-dose studies are warranted to evaluate pharmacokinetics at steady state in subjects with impaired renal function.

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LITERATURE CITED

1. **Akaike, H.** 1976. An information criterion (AIC). Math. Sci. **14**:5–9.
2. **Bothwell, W. M., K. S. Cathcart, and P. A. Bombardt.** 1989. An on-line, column-switching high-performance liquid chromatographic procedure for the removal of probenecid from human plasma, serum, or urine in the quantitative determination of cefmetazole or cefoxitin. J. Pharm. Biomed. Anal. **7**:987–995.
3. **Cornick, N. A., N. V. Jacobus, and S. L. Gorbach.** 1987. Activity of cefmetazole against anaerobic bacteria. Antimicrob. Agents Chemother. **31**:2010–2012.
4. **Gibaldi, M., and D. Perrier.** 1982. Pharmacokinetics, p. 63–72. Marcel Dekker, Inc., New York.
5. **Graves, D. A.** 1988. Failure of single-dose kinetics to predict steady state. Drug Intell. Clin. Pharm. **22**:917–918.
6. **Jones, R. N., A. L. Barry, P. C. Fuchs, and C. Thornsberry.** 1986. Antimicrobial activity of cefmetazole (CS-1170) and recommendations for susceptibility testing by disk diffusion, dilution, and anaerobic methods. J. Clin. Microbiol. **24**:1055–1059.
7. **Ko, H., K. S. Cathcart, D. L. Griffith, G. R. Peters, and W. J. Adams.** 1989. Pharmacokinetics of intravenously administered cefmetazole and cefoxitin and effects of probenecid on cefmetazole elimination. Antimicrob. Agents Chemother. **33**:356–361.
8. **Lee, C. C., and T. C. Marbury.** 1984. Drug therapy in patients undergoing hemodialysis: clinical pharmacokinetic considerations. Clin. Pharmacokinet. **9**:42–66.
9. **Levy, G.** 1977. Pharmacokinetics in renal disease. Am. J. Med. **62**:461–465.
10. **Metzler, C. M., G. L. Elfring, and A. J. McEwen.** 1974. A package of computer programs for pharmacokinetic modeling. Biometrics **30**:562–571.
11. **Nakao, H., H. Yanagisawa, B. Shimizu, M. Kaneko, M. Nagano, and S. Sugawara.** 1976. A new semisynthetic 7α-methoxycephalosporin, CS-1170: 7β-[[(cyanomethyl)thio]acetamido]-7α-methoxy-3-[[(1-methyl-1h-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic acid. J. Antibiot. **29**:554–558.
12. **Ohkawa, M., M. Orito, T. Sugata, M. Shimamura, M. Sawaki, E. Nakashita, K. Kuroda, and K. Sasahara.** 1980. Pharmacokinetics of cefmetazole in normal subjects and in patients with impaired renal function. Antimicrob. Agents Chemother. **18**:386–389.
13. **Ohm-Smith, M. J., and R. L. Sweet.** 1987. In vitro activity of cefmetazole, cefotetan, amoxicillin-clavulanic acid, and other antimicrobial agents against anaerobic bacteria from endometrial cultures of women with pelvic infections. Antimicrob. Agents Chemother. **31**:1434–1437.
14. **Rodriguez-Barbero, J., E. L. Mariño, and A. Dominguez-Gil.** 1985. Pharmacokinetics of cefmetazole administered intramuscularly and intravenously to healthy adults. Antimicrob. Agents Chemother. **28**:544–547.
15. **Shimada, J., Y. Hayashi, and K. Nakamura.** 1985. Cefmetazole: clinical evaluation of efficacy and safety in Japan. Drugs Exp. Clin. Res. **11**:181–194.