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Pharmacokinetics of Intravenously Administered Cefmetazole and Cefoxitin and Effects of Probenecid on Cefmetazole Elimination

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Sixteen healthy male volunteers participated in a randomized, balanced, three-way crossover study comparing the pharmacokinetics of cefmetazole, cefoxitin, and cefmetazole with probenecid pretreatment. Single 2-g doses of cefmetazole sodium and cefoxitin sodium were given intravenously as a 5-min infusion. Concentrations of cefmetazole and cefoxitin were determined by using a specific semiautomated high-performance liquid chromatographic method. Concentration-time profiles of cefmetazole and cefoxitin declined in a biexponential manner from peak levels. Compared with cefoxitin, cefmetazole had a significantly ($P < 0.05$) higher mean (± standard error of the mean) peak concentration in serum (290 ± 11 versus 244 ± 10 μg/ml), a longer terminal disposition half-life (1.50 ± 0.14 versus 0.81 ± 0.04 h), lower systemic clearance (111.7 ± 4.7 versus 279 ± 12 ml/min) and renal clearance (78.7 ± 4.3 versus 221 ± 14 ml/min) of intact drug, and a slightly smaller steady-state volume of distribution (10.3 ± 0.21 versus 12.8 ± 0.48 liters). Mean recoveries of cefmetazole and cefoxitin in urine were approximately 71 and 77%, respectively. Pretreatment of volunteers with probenecid (1 g orally) significantly ($P < 0.05$) increased concentrations of cefmetazole in serum 1 h after drug administration without significantly increasing maximum concentrations in serum. Mean areas under the concentration-time curve (466 ± 27 versus 295 ± 13 μg · h/ml) and terminal disposition half-lives (2.27 ± 0.13 versus 1.50 ± 0.14 h) of cefmetazole increased. Systemic clearance (72.1 ± 4.0 versus 111.7 ± 4.7 ml/min) and renal clearance (47.4 ± 4.0 versus 78.7 ± 4.3 ml/min) of intact antibiotic decreased. Mean recoveries (65.9 ± 3.7 versus 71.0 ± 3.2%) of intact cefmetazole in urine were not significantly ($P > 0.05$) different. Elimination of cefmetazole in urine was also significantly prolonged by probenecid, with substantial concentrations of cefmetazole (≧20 μg/ml) found in the 12- to 24-h urine collection for 14 of 16 volunteers. The results show that cefmetazole remains at clinically relevant concentrations (1 to 2 μg/ml) approximately twice as long as cefoxitin, that serum cefmetazole can be maintained longer at clinically significant concentrations with preadministration of probenecid, and that cefmetazole is partially eliminated by renal tubule secretion.

Cefmetazole sodium is a semisynthetic derivative of cephamycin C (5) having a very broad antibacterial spectrum in vivo and in vitro, including the majority of clinically important gram-positive and gram-negative aerobic and anaerobic bacteria (4). The MICs of cefmetazole for a number of gram-positive and gram-negative organisms are in the range of 0.5 to 4.0 μg/ml (4, 12). Clinical studies have confirmed its effectiveness, when administered parenterally, in the treatment of a number of infections (12) and as a prophylaxis for prevention of postsurgical wound infection (9).

Pharmacokinetic studies in healthy human volunteers administered intravenous doses of cefmetazole sodium have been conducted in Japan (6) and Europe (7, 8). Single doses ranging up to approximately 2 g were administered in these studies as a bolus or as an infusion. After bolus injection, concentrations of cefmetazole in plasma near 300 μg/ml were achieved (8). Concentration-time curves of cefmetazole in serum were fit by a one-compartment open model (6) after infusion of cefmetazole sodium or by a two-compartment open model (7, 8) after bolus injection of cefmetazole sodium. Mean disposition half-lives ranging from approximately 0.8 to 1.8 h were reported. High recoveries of intact drug, 69 ± 7.7% of the dose, in urine specimens collected up to 6 h after drug administration were reported (6).

Cefoxitin, a cephamycin antibiotic with an antibacterial spectrum similar to that of cefmetazole, has served as a comparator drug in clinical studies and microbiological comparisons of cefmetazole (4). The pharmacokinetics of cefoxitin have been extensively investigated (10, 11). Concentration-time curves of cefoxitin were fit by a two-compartment open model after bolus injection or infusion of cefoxitin sodium (3, 7, 10, 11). Mean terminal disposition half-lives of cefoxitin ranged from 0.63 to 1.04 h in these studies, and recoveries from urine ranged from 74.1 to 111%. In the only study in which cefmetazole sodium and cefoxitin sodium were administered to the same volunteers (7), the terminal disposition half-lives of cefmetazole and cefoxitin were 1.8 and 1.04 h, respectively, when these drugs were administered concomitantly. No information is available as to whether these two drugs interact when administered concomitantly.

Probenecid, a drug that blocks renal tubular secretion of organic acids (1), markedly decreases renal clearance and increases the terminal disposition half-life of some cephamycins, e.g., cefoxitin (3). The effect of probenecid on cefmetazole disposition in humans has not yet been reported. In this study, the pharmacokinetics of cefmetazole and cefoxitin were directly compared, and the effects of probenecid on the renal tubule secretion and pharmacokinetics of cefmetazole were investigated in the same volunteers in a balanced crossover design.

MATERIALS AND METHODS

Volunteers. Sixteen healthy male volunteers participated in and completed the study after giving written informed consent. The ages of the volunteers ranged from 20 to 49

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years with a mean of 31 years. The heights of volunteers ranged from 166 to 186 cm with a mean of 175 cm, and weights varied from 61.0 to 105 kg with a mean of 76.7 kg. All volunteers weighed within 20% of their predicted ideal body weights. During the 2 weeks before drug administration, each of the volunteers was evaluated and had normal serum creatinine values, normal urinalysis findings, and normal liver chemistries (serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, total bilirubin, alkaline phosphatase). Volunteers were excluded if they had a prior history of allergy to penicillins, cephalosporins, or probenecid. Volunteers were not permitted to take any antibiotics for 30 days before the study, and no other therapy, including over-the-counter medications, was allowed for 7 days before the study.

Study design. Volunteers were randomly assigned in advance in an open, balanced three-way crossover of Latin-square design. Each volunteer received the three treatments with a 1-week washout period between each treatment period. For treatment A, probenecid (1 g) was administered orally, followed 30 min later by 2 g of cefmetazole administered intravenously. For treatment B, 2 g of cefmetazole was administered intravenously. For treatment C, 2 g of cefoxitin was administered intravenously. Identical drug lots were used for all treatment periods.

Volunteers fasted and did not drink fluids overnight (9 h) before each treatment period. Probenecid tablets (1 g of probenecid [Benemid]; Merck Sharp & Dohme, West Point, Pa.) were administered with 4 oz. (ca. 118.3 ml) of water. Vials of cefmetazole sodium (2 g of cefmetazole [Zefazone]; The Upjohn Co., Kalamazoo, Mich.) and cefoxitin sodium (2 g of cefoxitin [Mefoxin]; Merck Sharp & Dohme) were used. The antibiotics were dissolved in distilled water and diluted to 20 ml with physiological saline before administration. The solution of antibiotic was infused into a peripheral vein over 5 min with an I-MED infusion pump (I-MED Corp., San Diego, Calif.).

Laboratory tests on blood and urine were conducted before each drug dose and 24 h after the final drug dose. Vital signs (supine blood pressure, pulse, respirations, and temperature) were measured just before and at 5, 30, and 60 min after each drug administration. Volunteers were asked about any adverse medical events just before each drug dose and at regular intervals thereafter until 24 h after dosing.

Specimen collection. Blood specimens (10 ml) for the measurement of antibiotic levels were obtained by individual venipuncture from the antecubital vein in the arm opposite the site of drug administration. Specimens were collected immediately before and 0.083, 0.167, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after each antibiotic administration. Specimens were allowed to clot for 30 min, and then serum was collected and immediately frozen at −20°C for later analysis. All urine excreted was collected for the 12-h interval immediately before drug administration (i.e., −12 to 0 h) and for the intervals 0 to 1, 1 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h in relation to antibiotic administration. The urine specimens were kept on ice during collection. After thorough mixing of and interval collection, the urine volume was recorded, and a sample was removed and frozen at −20°C for later analysis.

Drug analysis. The concentrations of cefmetazole and cefoxitin in 1-ml samples of serum and urine were determined by using a specific semiautomatic high-performance liquid chromatographic method (W. Bothwell and P. Bombardt, submitted for publication). Serum proteins were precipitated with trichloroacetic acid. Column switching eliminated the need for long chromatographic run times because of the long retention times of probenecid under the conditions used. Probenecid was retained on a precolumn after sample injection, whereas cefmetazole, cefoxitin, and the internal standard were eluted onto the analytical column. The probenecid was then shunted to waste by reversing the direction of flow of the mobile phase on the precolumn. When necessary, specimens were diluted into the range of the standard curve with control serum or urine. Concentrations of cefmetazole and cefoxitin were expressed in acid equivalents.

Noncompartmental pharmacokinetic analysis. Semilogarithmic plots of cefmetazole and cefoxitin serum concentration-time curves were constructed, and the terminal disposition rate constant (β) for each curve was calculated by log-linear regression analysis of the last four measurable concentrations in the terminal disposition phase. The corresponding disposition half-life ($t_{1/2\beta}$) was calculated by the equation $t_{1/2\beta} = \ln(2)/\beta$. Areas under the serum concentration-time curve (AUC) and under the first-moment curve (AUMC) were determined from the beginning of infusion to the last measurable concentration in serum by trapezoidal rule and then extrapolated to infinite time (2). The extrapolated AUC was calculated by dividing the last measurable concentration in serum by the terminal disposition rate constant from fits of two-compartment open models to concentration-time data. Volumes of distribution at steady state [$V_{ss} = (D \times \text{AUMC})/(\text{AUC})^2 - (T \times D)/(2 \times \text{AUC})$] and systemic clearances ($CL = D/\text{AUC}$) were calculated by standard procedures (2), where D is the dose of antibiotic administered over the infusion interval T. Renal clearances of intact drug were calculated for each urinary excretion interval and for cumulative urinary excretion intervals by using the expression $CL_R = (X_u^{1-2})/(AUC_{t1-t2})$, where X_u^{1-2} is the amount of intact antibiotic excreted in urine during the time interval $t1$ to $t2$ and AUC_{t1-t2} is the AUC of the antibiotic during that time interval.

Compartmental pharmacokinetic analysis. Concentration-time data for cefmetazole and cefoxitin in serum were fitted by one-, two-, and three-compartment open models with zero-order input and first-order distribution and elimination by using the computer programs NONLIN (C. M. Metzler, G. L. Elfring, and A. J. McEwen, Biometrics **30**:562, 1974) and NONLIN84 (C. M. Metzler and D. L. Weiner, NONLIN84 User's Guide, version V02; 1984; Statistical Consultants, Inc., Edgewood, Ky.). The effects of the weighting functions 1, $1/C$, and $1/C^2$ on the calculated model parameters were studied, where C is the experimentally determined concentration of the antibiotic in serum. The goodness of fit of a model for the different weights was determined by visual comparison. The goodness of fits of the one-, two- and three-compartment open models was compared by the F test, namely, the mean difference in the residual sums of squares of the models was compared with the mean residual sum of squares of the model with the larger number of parameters.

Statistical analysis. The data were analyzed for significant effects by using the Duncan multiple-range test in the general linear models program of the Statistical Analysis System (version 5.16; SAS Institute, Gary, N.C.). A linear model included volunteers, treatment periods, and treatments as main effects. Analyses were carried out on the untransformed parameters. The decision point probability for statistical significance was set at $P = 0.05$.

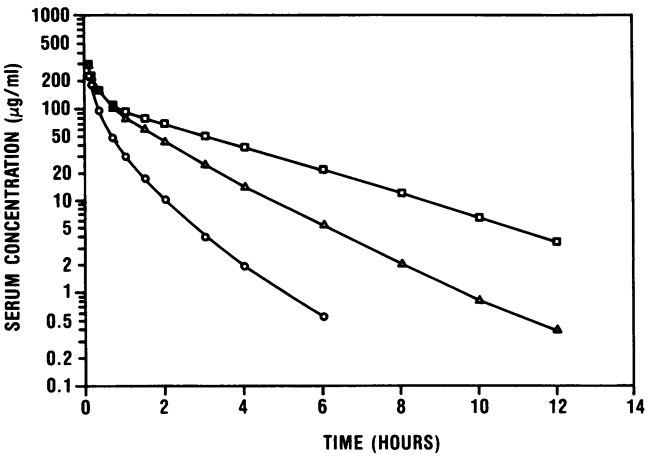

FIG. 1. Mean concentration-time profiles of cefmetazole and cefoxitin in serum after intravenous infusion (5 min) of 2-g doses of cefmetazole sodium (△), cefoxitin sodium (○), and cefmetazole sodium after pretreatment with 1 g of orally administered probenecid (□).

RESULTS

Clinical results. All volunteers tolerated the drug treatments well. The most frequent complaints were mild discomfort at the intravenous catheter sites, nasal congestion, and headache. No significant changes in vital signs or laboratory test results were noted.

Drug analysis. The linearity of response of calibration curve data for the antibiotics in serum or urine was tested by using unweighted linear regression analysis. No significant deviations from linearity were revealed for concentrations of cefmetazole and cefoxitin in serum up to 200 μg/ml or in urine up to 1 mg/ml. Correlation coefficients were greater than 0.995 (n = 15) and 0.999 (n = 16) for standard curves of cefmetazole and cefoxitin in serum, respectively. Values greater than 0.999 (n = 9) and 0.998 (n = 9) were calculated for the respective standard curves of cefmetazole and cefoxitin in urine. Intercepts of the standard curves were not significantly different from zero ($P > 0.05$) for most curves. The lower limits of quantitation were approximately 1.5 and 0.9 μg/ml for cefmetazole and cefoxitin in serum, respectively, and approximately 12 and 8 μg/ml for cefmetazole and cefoxitin in urine, respectively.

Precision and accuracy of analyses were determined over the concentration range of interest. Replicate samples of control serum and urine, fortified with cefmetazole and cefoxitin at three different concentrations, were analyzed. In serum, mean recoveries of cefmetazole and cefoxitin ranged from 95.9 to 100.2%. Between-day coefficients of variation were less than 8.4% for concentrations in serum ranging from 4.8 to 122 μg/ml. In urine, mean recoveries of cefmetazole and cefoxitin ranged from 97.6 to 105.2%. Between-day coefficients of variation were less than 3.8% for concentrations in urine ranging from 60 to 600 μg/ml.

Noncompartmental pharmacokinetic analysis. The serum samples obtained from the 16 volunteers were analyzed for intact antibiotic. Mean concentration-time profiles of cefmetazole and cefoxitin in serum are shown in Fig. 1 for the three treatments. Measurable cefoxitin concentrations in serum were significantly lower than the corresponding cefmetazole concentrations in serum at all collection times ($P < 0.05$), and cefmetazole concentrations remained at clinically relevant levels (1 to 2 μg/ml) approximately twice as long as cefoxitin concentrations.

The mean terminal disposition half-lives of cefmetazole and cefoxitin, calculated by log-linear regression analysis of the final four measurable concentration-time points of each treatment, are given in Table 1. Mean noncompartmental pharmacokinetic parameters and associated standard errors are also shown. Compared with cefoxitin, the mean AUC and terminal disposition half-life of cefmetazole were significantly greater ($P < 0.05$), and the systemic clearance of cefmetazole was significantly lower ($P < 0.05$).

Treatment of volunteers with probenecid before cefmetazole sodium administration did not significantly change ($P > 0.05$) peak concentrations of cefmetazole in serum (306 versus 290 μg/ml). However, concentrations of cefmetazole in serum at all collection times greater than 1 h after antibiotic administration were consistently higher ($P < 0.05$) and remained at clinically relevant levels approximately twice as long after probenecid pretreatment. Mean AUC (466 versus 295 μg · h/ml) and terminal disposition half-life (2.27 versus 1.50 h) were significantly greater ($P < 0.05$) and systemic clearance (72.1 versus 112 ml/min) was significantly lower ($P < 0.05$) after probenecid pretreatment.

Concentrations of cefmetazole as high as 25.7 mg/ml were observed in urine over the first 4 h after drug administration (range, 0.158 to 25.7 mg/ml), and concentrations in excess of 100 μg/ml were observed over the 4- to 8-h urine collection interval (range, 458 to 1,570 μg/ml). Clinically relevant concentrations of cefmetazole (1 to 2 μg/ml) persisted in urine over the 8- to 12-h urine collection interval (range, 7 to 88 μg/ml). In contrast, substantial concentrations of cefoxitin were generally not observed in urine after the 4- to 8-h urine collection interval. Visual comparison of cumulative recovery curves in urine indicated that renal elimination of cefoxitin was more rapid than renal elimination of cefmetazole (Fig. 2). Thus, renal clearance of cefoxitin was substantially higher than that of cefmetazole (221 versus 78.7 ml/min) (Table 1). Nearly 50% of the cefmetazole sodium dose was recovered in the urine as intact drug within 2 h

TABLE 1. Noncompartmental pharmacokinetic parameters for cefmetazole (with and without probenecid pretreatment) and cefoxitin[a]

Treatment[b]	C_{max} (μg/ml)	$t_{1/2\beta}$ (h)	V_{ss} (liters)	AUC (μg · h/ml)	Urinary recovery (%)	CL (ml/min)	CL_R (ml/min)
A	306 ± 16	2.27[c] ± 0.13	12.6[c] ± 0.53	466[c] ± 27	65.9 ± 3.7	72.1[c] ± 4.0	47.4[c] ± 4.0
B	290 ± 11	1.50 ± 0.14	10.3 ± 0.21	295 ± 13	71.0 ± 3.2	111.7 ± 4.7	78.7 ± 4.3
C	244[d] ± 10	0.81[d] ± 0.04	12.8[d] ± 0.48	129[d] ± 5.4	76.7 ± 5.2	279[d] ± 12	221[d] ± 14

[a] Values are means ± standard error of the mean. C_{max}, Maximum concentration in plasma; CL, total clearance; CL_R, renal clearance.
[b] A, Cefmetazole sodium, 2-g intravenous dose; probenecid pretreatment, 1-g oral dose. B, Cefmetazole sodium, 2-g intravenous dose. C, Cefoxitin sodium, 2-g intravenous dose.
[c] $P < 0.05$, treatment A versus treatment B.
[d] $P < 0.05$, treatment C versus treatment B.

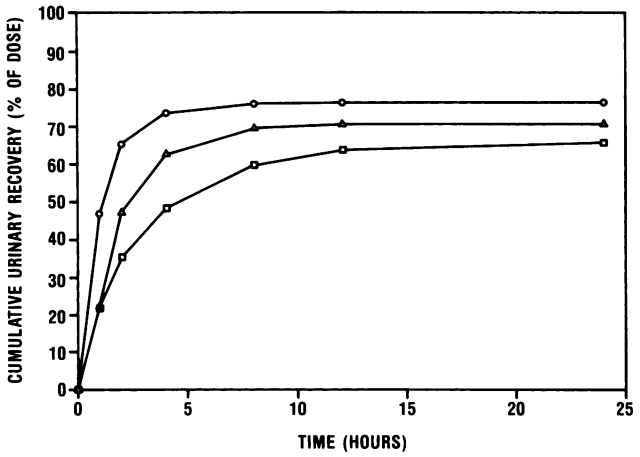

FIG. 2. Mean cumulative recovery of cefmetazole and cefoxitin in urine after intravenous infusion (5 min) of 2-g doses of cefmetazole sodium (△), cefoxitin (○), and cefmetazole sodium after pretreatment with 1 g of orally administered probenecid (□).

after drug administration, and nearly all of the drug excreted in urine was recovered within 8 h after dosing. By comparison, nearly all of the cefoxitin sodium dose was recovered within 4 h after dosing. In this study, the mean cumulative recoveries of cefmetazole and cefoxitin from urine (71.0 versus 76.7%) were not significantly different ($P > 0.05$).

When volunteers were pretreated with probenecid before cefmetazole sodium was administered, excretion of cefmetazole in urine was prolonged so that clinically relevant concentrations of cefmetazole were excreted in the 12- to 24-h urine collection interval (range, 20 to 169 μg/ml). Visual comparison of the cumulative recovery curves (Fig. 2) indicated that treatment with probenecid before administration of cefmetazole sodium slows the renal elimination of cefmetazole. Thus, renal clearance of intact cefmetazole (47.4 versus 78.7 ml/min) was significantly reduced ($P < 0.05$) when the drug was administered after pretreatment with probenecid. The majority of the drug was recovered within 12 h, and pretreatment with probenecid did not significantly ($P > 0.05$) alter the mean cumulative recovery of intact cefmetazole from urine (65.9 versus 71.0%).

Compartmental pharmacokinetic analysis. One-, two- and three-compartment models were fit to cefmetazole and cefoxitin serum concentration-time data by using a weighting function of $1/C$. The two-compartment open model fit the data for all treatments significantly better (F statistic, $P < 0.001$) than did the one-compartment open model. The three-compartment open model fit the data significantly better ($P < 0.05$) than did the two-compartment open model only in the case of two or three subjects from each treatment. Consequently, the two-compartment model was adopted as the most appropriate pharmacokinetic model for the cefmetazole and cefoxitin serum concentration-time data. Visual comparison of model fits indicated that a weighting function of $1/C$ provided the best overall fits of the concentration-time curves.

Compartmental pharmacokinetic parameters, including disposition rate constants and half-lives, were obtained by fitting the two-compartment infusion model to the serum concentration-time data of each volunteer for treatments A, B, and C. Mean compartmental pharmacokinetic parameters and disposition rate constants and half-lives are summarized in Table 2. Terminal disposition half-lives calculated by fitting data with the two-compartment model were generally in excellent agreement with those calculated by log-linear regression analysis.

Statistical comparison of cefmetazole and cefoxitin compartmental pharmacokinetic parameters indicated that k_{21} and the disposition rate constant (α) were not significantly different ($P > 0.05$), that V_1, k_{10}, and β were significantly greater ($P < 0.05$), and that k_{12} was significantly smaller ($P < 0.05$) for cefoxitin.

Comparison of cefmetazole compartmental pharmacokinetic parameters indicated that small and statistically insignificant ($P > 0.05$) changes occurred in the volume of distribution of the central compartment (V_1, 6.03 versus 5.59 liters) and the rate constant for the transfer of drug from the tissue compartment (k_{21}, 2.27 versus 2.13 per h) after pretreatment of volunteers with probenecid. A large change did occur in the rate constant for the transfer of drug to the tissue compartment (k_{12}, 1.94 versus 3.86 per h), suggesting that probenecid caused substantial changes in the distribution of cefmetazole in tissue even though this change was not statistically significant ($P > 0.05$) because of the high variability in k_{12}. The elimination rate constant (k_{10}) and terminal disposition rate constant (β) for cefmetazole were significantly smaller ($P < 0.05$) and the corresponding half-lives, $t_{1/2k_{10}}$ and $t_{1/2\beta}$, were significantly larger after pretreatment with probenecid. Comparison of the magnitude of the changes in k_{10} (1.17 versus 0.864 per h) and β (0.557 versus 0.307 per h) indicated that the decrease in β (45%) was nearly twice that in k_{10} (26%). These results indicate that probenecid causes substantial changes in cefmetazole tissue distribution and elimination, since in a two-compartment model the terminal disposition rate constant is a hybrid constant that is a function of both the elimination and distribution rate constants (2). In fact, the fraction of the cefmetazole dose in the central compartment during the β phase, $fc = (k_{21} - \beta)/(k_{21} + k_{12} - \beta)$, decreased from 50 to 32% after pretreatment with probenecid.

Noncompartmental pharmacokinetic parameters were also calculated by using the two-compartment model parameters. Excellent agreement was found between parameters calculated by noncompartmental techniques directly from

TABLE 2. Mean compartmental pharmacokinetic parameters for two-compartment model fits of serum cefmetazole and cefoxitin concentrations (weighting, $1/C$)[a]

Treatment[b]	V_1 (liters)	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{10} (h^{-1})	α (h^{-1})	$t_{1/2\alpha}$ (h)	β (h^{-1})	$t_{1/2\beta}$ (h)
A	5.59 ± 0.32	3.86 ± 1.20	2.13 ± 0.16	0.864[c] ± 0.090	6.55 ± 1.35	0.141 ± 0.014	0.307[c] ± 0.014	2.33[c] ± 0.10
B	6.03 ± 0.25	1.94 ± 0.30	2.27 ± 0.16	1.17 ± 0.062	4.82 ± 0.45	0.161 ± 0.012	0.557 ± 0.016	1.26 ± 0.040
C	7.50[d] ± 0.31	1.53 ± 0.23	1.78[d] ± 0.13	2.33[d] ± 0.12	4.76 ± 0.42	0.162 ± 0.012	0.880[d] ± 0.032	0.805[d] ± 0.030

[a] Values are means ± standard error of the mean.
[b] See footnote *b* of Table 1; $n = 16$.
[c] $P < 0.05$, treatment A versus treatment B.
[d] $P < 0.05$, treatment B versus treatment C.

experimental data and those derived from the two-compartment model parameters.

DISCUSSION

The pharmacokinetics of cefmetazole and cefoxitin have previously been described after bolus intravenous injection or intravenous infusion. After bolus intravenous injection, a two-compartment open model with first-order intercompartmental drug transfer and first-order elimination was reported to fit concentration-time curves of cefmetazole (7, 8) and cefoxitin (3, 7, 10, 11) better than did a one-compartment model. In the only previously reported pharmacokinetic study in which cefmetazole sodium was administered as an intravenous infusion, concentration-time curves were fitted by using a one-compartment open model with first-order elimination (6). In this study, terminal disposition half-lives calculated by fitting the serum concentration-time data with a one-compartment open model were significantly shorter than those calculated by log-linear regression analysis, unless a weighting function inversely proportional to the square of the concentration was used. In the latter case, the one-compartment model fitted the terminal portion of the curves very well, but peak concentrations in serum were grossly underestimated. These visual observations were confirmed by statistical comparisons, which indicated that serum concentration-time curves for cefmetazole and cefoxitin after a 5-min infusion of both drugs were best described by a two-compartment open model, in agreement with previous investigations in which these drugs were administered by bolus intravenous injection.

When compared with those of cefoxitin, concentrations of cefmetazole in serum were significantly higher from the termination of infusion to the last measurable concentration. Similar results were found in the comparative pharmacokinetics study conducted by Rodriguez-Barbero et al. (7), in which both drugs were administered concomitantly. The mean terminal disposition half-life of cefmetazole found in this study was considerably longer than that of cefoxitin (1.50 ± 0.14 versus 0.81 ± 0.04 h; $n = 16$), consistent with the study of Rodriguez-Barbero et al. (7). However, the mean terminal disposition half-lives of cefmetazole and cefoxitin found in this study were systematically lower by 30 and 20%, respectively, than those reported by Rodriguez-Barbero et al. (7). A shorter terminal disposition half-life was reported for cefmetazole by Ohkawa et al. (6) (0.81 ± 0.08 h; $n = 5$), who fitted the concentration-time data with a one-compartment open model. The mean terminal disposition half-life of cefoxitin found in this study was in excellent agreement with previously reported values (8, 10, 11). This study definitively demonstrates that systemic concentrations of cefmetazole persist approximately twice as long as comparable cefoxitin concentrations. Since in vitro susceptibility tests (4) indicate that cefmetazole MICs are generally less than or equal to those of cefoxitin for most strains of bacteria, intravenously administered cefmetazole sodium should require equal or less frequent administration than that required with cefoxitin sodium to achieve comparable efficacy.

The mean cumulative recovery of intact cefmetazole in urine in this study (71%) was comparable to that reported in the study by Ohkawa et al. (6) (69%), in which urine was collected for 6 h after drug administration. The present study indicated that elimination of cefmetazole in urine was essentially complete in 8 h, but substantial concentrations of cefmetazole continued to be excreted in urine over the 8- to 12-h urine collection interval. Previous investigators (10, 11) found that 75 to 95% of the cefoxitin dose was excreted in the urine as intact drug, consistent with the 76% recovery of intact cefoxitin found in this study. Elimination of cefoxitin in urine was essentially complete within 4 h after drug administration, and substantial concentrations of cefoxitin were generally not found in urine after the 4- to 8-h urine collection interval. The mean renal clearance of intact cefmetazole calculated in this study was less than that reported in the study by Ohkawa et al. (6), in which five volunteers with normal renal function were enrolled. The more rapid renal clearance found by Ohkawa et al. was consistent with the shorter terminal disposition half-life found in that study. Previous investigators reported renal clearances of cefoxitin ranging from 206 to 322 ml/min per 1.73 m^2 after administration of 2-g doses of cefoxitin sodium to apparently healthy volunteers (10, 11), in good agreement with the results of this study. All of these studies are consistent in indicating that the renal clearance of cefoxitin is at least twice that of cefmetazole. Since the recoveries of cefmetazole and cefoxitin in urine are very similar and the renal clearance of cefoxitin is at least twice that of cefmetazole, significant antibacterial concentrations of cefmetazole persist in urine longer than do significant concentrations of cefoxitin.

Consistent with results previously reported for cefoxitin (3), pretreatment of normal volunteers with probenecid significantly decreased systemic and renal clearances of cefmetazole. In fact, the terminal disposition half-life was nearly twice that observed when cefmetazole sodium was administered without probenecid pretreatment, and concentrations of cefmetazole in serum and urine remained high for more than 12 and 24 h, respectively, in most subjects. These results indicate that cefmetazole concentrations can be maintained at clinically relevant levels in serum and urine approximately twice as long with concomitant administration of probenecid. Administration of probenecid before cefmetazole sodium can be considered in clinical situations in which levels of drug in blood and/or urine need to be maintained at high levels for prolonged periods.

After pretreatment of volunteers with probenecid, the elimination half-life ($t_{1/2k_{10}}$) of cefmetazole increased approximately 25%, indicating that elimination of cefmetazole is inhibited by probenecid and that the drug is at least partially eliminated by renal tubule secretion. However, the relative magnitude of the change in $t_{1/2k_{10}}$ was considerably smaller than those found for several other antibiotics (1). Furthermore, the relative magnitude of the increase in the terminal disposition half-life ($t_{1/2\beta}$) was much greater (84%) than the increase in $t_{1/2k_{10}}$ (25%), in opposition to the pharmacokinetic results reported for several other antibiotics (1). In the previously reported studies, a large increase in the elimination half-life of the drug was counterbalanced by a correspondingly large increase in the fraction of the drug available in the central compartment for elimination (i.e., the apparent volume of distribution of the drug significantly decreased) after concomitant administration of probenecid. Consequently, the change in the terminal disposition half-life of the drug was small relative to the change in the elimination half-life. In the case of cefmetazole, the half-life of elimination from the central compartment increased and the fraction of drug available for elimination decreased after pretreatment with probenecid. Hence, both elimination and distribution contributed to the long terminal disposition half-life of cefmetazole. The net results were significantly ($P < 0.05$) decreased systemic and renal clearances and a significant (P

< 0.05) increase in the steady-state volume of distribution after pretreatment of volunteers with probenecid.

In conclusion, this study has definitively shown that cefmetazole is at least partially eliminated by renal tubule secretion, that cefmetazole concentrations can be maintained at clinically relevant levels (1 to 2 μg/ml) in serum and urine approximately twice as long by pretreatment with probenecid, and that cefmetazole remains at clinically relevant levels in serum and urine approximately twice as long as does cefoxitin.

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