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Comparative Multiple-Dose Pharmacokinetics of Cefotaxime, Moxalactam, and Ceftazidime

RUEDI LÜTHY,[1]* JÜRG BLASER,[1,2] ANTONIO BONETTI,[1] HANSPETER SIMMEN,[1] RICHARD WISE,[3] AND WALTER SIEGENTHALER[1]

Department of Medicine, University of Zürich,[1] Institute for Biomedical Engineering, University of Zürich and Federal Institute of Technology,[2] CH-8091 Zürich, Switzerland, and Department of Medical Microbiology, Dudley Road Hospital, Birmingham, United Kingdom[3]

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The pharmacokinetics of cefotaxime, moxalactam, and ceftazidime were investigated in six human volunteers who received in a crossover fashion doses of 0.5, 1.0, and 2.0 g of each drug by a 5-min infusion. Doses of 1.0 g were repeated after the administration of probenecid. Serum and urine concentrations were assayed with an agar diffusion method. Serum concentrations of moxalactam exceeded those of ceftazidime at all times and were distinctly higher than those of cefotaxime. The normalized area under the concentration time curve (defined as the ratio of the area under the curve per dose) reflects this relationship: compared with cefotaxime the normalized area under the curve of moxalactam was 3 to 4 times higher, and that of ceftazidime was 2 to 3 times higher. By intra-individual comparisons, the area under the curve of moxalactam was 44% larger than that of ceftazidime. With increasing doses, cefotaxime exhibited a nonlinear increase of the area under the curve. The half-lives of moxalactam, ceftazidime, and cefotaxime were 2.34, 1.95, and 1.16 h, respectively. The volume of distribution averaged 0.20 ± 0.03, 0.23 ± 0.02, and 0.25 ± 0.04 liters per kg, and the mean total body clearance was 84, 131, and 328 ml/min for moxalactam, ceftazidime, and cefotaxime, respectively. The 24-h urinary recovery was highest for moxalactam (75 ± 4%) followed by ceftazidime (68 ± 11%) and cefotaxime (53 ± 6%). The influence of probenecid on serum concentrations, half-life, area under the curve, and clearance was most apparent with cefotaxime, whereas the pharmacokinetics of moxalactam and ceftazidime were only slightly affected. After the 0.5- and 2.0-g doses of cefotaxime, desacetyl-cefotaxime activity (determined by high-pressure liquid chromatography) reached a peak of 2.7 and 9.9 μg/ml and declined with a half-life of 1.9 and 1.4 h. The ratio of the R(−) and S(−) epimers of moxalactam, which could be differentiated by high-pressure liquid chromatography, fell rapidly from 0.81 at 0.17 h to 0.5 at 5 h, indicating the presence of twice as much of the microbiologically less active S(−) epimer. From a pharmacokinetic standpoint it appears reasonable to conclude that moxalactam and possibly ceftazidime could be administered twice daily and that cefotaxime could be administered three or even four times daily.

Cefotaxime (CTX), moxalactam (MOX), and ceftazidime (CAZ) (GR-20263) are semisynthetic parenteral cephalosporins with relatively high activities against gram-negative organisms and considerable stability against their β-lactamases (4, 5, 8, 11). Despite quantitative differences in activity against certain species, their antimicrobial spectra are very similar. Therefore, differences in pharmacokinetic behavior may well be a decisive factor in the physicians' choice of any of these three compounds.

The purposes of the present study were to: (i) compare the pharmacokinetics of three different doses of CTX, MOX, and CAZ; (ii) evaluate the influence of probenecid on the pharmacokinetics of these three compounds; (iii) determine the linearity of dose response; (iv) compare the serum kinetics of the R(−) and S(−) epimers of MOX; (v) evaluate the pharmacokinetics of the desacetyl metabolite of CTX (DES-CTX); and (vi) compare agar diffusion and high-pressure liquid chromatography (HPLC) assays for CTX and MOX.

(These results were presented in part at the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., 22 through 24 September 1980.)

MATERIALS AND METHODS

Six healthy male medical students with a mean

weight of 69 kg (range, 64 to 73 kg) took part in the study. Informed consent according to institutional policies was obtained from each participant. The antibiotics (laboratory reference standards and material for injection) were supplied by the following companies: CTX was from Hoechst AG, Frankfurt, West Germany; MOX was from Eli Lilly GmbH, Bad Homburg, West Germany, and CAZ was from Glaxo Group Research Limited, Greenford, United Kingdom.

At intervals of 2 weeks 0.5, 1.0, and 2.0 g of CTX and MOX were administered by a 5-min intravenous infusion in crossover fashion to each participant. The infusion rate was controlled with an infusion pump (Perfusor E+2; Braun Melsungen, West Germany). The 1.0-g doses were repeated after five doses of oral probenecid (0.5 g every 6 h on the day before the study and 1.0 g 30 min before the dose). Four months later the same doses of CAZ were administered under the same study protocol.

During each study blood samples were drawn through an indwelling winged needle placed in the forearm contralateral to the infusion site at 0, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h. Blood specimens were centrifuged at 4°C after clotting at room temperature. In addition, urine was collected quantitatively over six time intervals (−24 through 0, 0 through 2, 2 through 4, 4 through 8, 8 through 12, and 12 through 24 h after administration).

The exact amount of antibiotic administered to each volunteer was determined (Fig. 1 and 2). The exact volume delivered by the infusion pump during a 5-min period was weighed on an analytical balance after each administration; subsequently the antibiotic concentration of the infusate was diluted appropriately, divided in four aliquots, and assayed as outlined below. Serum and urine standards in the range of expected concentrations were prepared on the day of each study from pooled antibiotic-free human serum and 0.05 M phosphate-buffered saline (pH 7.0), respectively. The latter was also used to dilute urine samples to obtain concentrations below 256 μg/ml. All samples and standards were immediately frozen in liquid nitrogen and assayed in quintuplicates within 2 weeks by the large plate agar diffusion method of Bennett et al. (1). The assay strain for CTX (a *Proteus morganii* strain obtained from D. S. Reeves, Bristol, United Kingdom) was resistant to ≦16 μg of DES-CTX per ml. *Escherichia coli* strain ATCC 10536 was used to determine MOX serum and urine concentrations in the range of 1 to 256 μg/ml, a clinical isolate of *Klebsiella pneumoniae* was used for concentrations between 0.125 and 1 μg/ml, and a *P. morganii* strain obtained from Glaxo served as the assay organism for CAZ. The precision of this assay was considerably improved when serum and urine samples of CAZ, including the appropriate standards, were diluted in 0.05 M phosphate-buffered saline (pH 7.0) to obtain final concentrations between 0.5 and 16 μg/ml. To determine the precision of the microbiological assay, 10 to 25 spiked serum and 0.05 M phosphate-buffered saline samples in the range of expected concentrations (0.125 to 256 μg/ml) were prepared for each antibiotic and subsequently measured in quintuplicates on three different occasions. For each concentration the coefficient of variation was then determined from this set of three measurements. The mean values (± standard deviation) obtained over the entire range of concentrations were 4.4 ± 1.1, 5.0 ± 0.6, and 4.4 ± 1.6% for CTX, MOX, and CAZ, respectively.

Serum samples of the 0.5- and 2.0-g doses of CTX and MOX were also analyzed by a HPLC method (15, 16). Its sensitivity limit is ≧1 μg/ml, and the 95% confidence limits are ≦15%. In addition, the comparison of the agar diffusion and the HPLC assays permitted an estimate of the accuracy of the two methods. The latter provided information on the behavior of DES-CTX and the two naturally occurring epimers of MOX. HPLC analyses were performed by R. Wise, Birmingham, United Kingdom.

Before, during, and after each study period the following tests were performed: complete blood count, urea, serum and urine creatinine, total protein, bilirubin, transaminases, alkaline phosphatase, and urinalysis. Volunteers were questioned about side effects after each study.

Pharmacokinetic analysis. A two-compartment open model was used to describe the serum concentration time courses (3). The pharmacokinetic parameters of the model, volume of distribution of the central compartment (V_1), rate constants of transfer between the two compartments (k_{12} and k_{21}), and rate constant of elimination (k_e) were adapted to the experimental data with a nonlinear fitting program by minimizing the sum of weighted squared deviations (7). The weighting function of the residuals between observed and predicted values was derived from the analysis of precision of the bioassay which yielded a constant relative error. The terminal half-life ($t_{1/2}$) was then defined by these parameters. The total volume of distribution (V_D), total body clearance (Cl_B), and total renal clearance (Cl_R) were calculated by the following equations: $V_D = V_1 (1 + k_{12}/k_{21})$, $Cl_B = V_1 k_e$, and $Cl_R = Cl_B \cdot feU$, where feU is the excreted urinary fraction of the administered dose. The areas under the serum concentration time curves (AUC) were estimated by the trapezoidal rule. To facilitate comparisons among the various doses and drugs, AUCs were normalized by dividing through the individual doses. For all statistical evaluations the Wilcoxon matched-pairs signed rank test was used. Probabilities of $2\alpha \leqq 0.05$ were considered significant.

Because of inappropriate infusion in one of 72 drug administrations the data from one volunteer who was given the 2.0-g dose of CAZ were excluded from the above calculations.

RESULTS

Serum kinetics by bioassay analysis. The mean serum concentrations of CTX, MOX, and CAZ are presented in Fig. 1 and 2. At 6, 8, and 12 h serum concentrations of CTX were frequently below the lowest standard (0.125 μg/ml). Figure 1 shows a comparison of the mean serum concentrations of CTX, MOX, and CAZ of the 0.5- and 2.0-g doses. It is evident that MOX achieved the highest concentrations at all dose levels, followed by CAZ and CTX. At 2 h after injection, serum levels after 0.5-g doses of MOX

TABLE 1. *Synopsis of pharmacokinetic parameters of CTX, MOX, and CAZ*[a]

Drug	Dose (g)	V_1 (liters/kg)	V_D (liters/kg)	k_{12} ($\times 10^{-4}$/h)	k_{21} ($\times 10^{-4}$/h)	$t_{1/2}$ (h)	Cl_B (ml/min)	*feU* (%)	Cl_R (ml/min)	Cl_{CR} (ml/min)	Cl_R/Cl_{CR}
CTX	0.5	0.17 ± 0.04	0.29 ± 0.05	2.30 ± 1.10	3.05 ± 1.12	1.10 ± 0.38	391 ± 97	58 ± 12	217 ± 31	129 ± 18	1.69 ± 0.11
	1.0	0.14 ± 0.03	0.24 ± 0.04	2.10 ± 0.72	2.98 ± 0.85	1.08 ± 0.27	326 ± 48	47 ± 7.9	154 ± 38	132 ± 16	1.16 ± 0.22
	2.0	0.15 ± 0.02	0.21 ± 0.04	1.00 ± 0.43	2.13 ± 0.73	1.31 ± 0.32	267 ± 49	56 ± 18	145 ± 48	141 ± 18	1.03 ± 0.29
	1.0 + P[b]	0.10 ± 0.01	0.18 ± 0.02	3.40 ± 0.82	3.97 ± 0.55	1.15 ± 0.03	169 ± 16	51 ± 3.6	85 ± 8.8	124 ± 10	0.69 ± 0.10
MOX	0.5	0.09 ± 0.01	0.18 ± 0.01	2.45 ± 0.60	2.63 ± 0.73	2.35 ± 0.32	77.8 ± 9.4	79 ± 4.8	61.7 ± 9.0	135 ± 18	0.46 ± 0.06
	1.0	0.10 ± 0.01	0.19 ± 0.01	3.35 ± 1.18	3.47 ± 1.03	2.25 ± 0.21	81.2 ± 10.6	71 ± 7.3	58.0 ± 9.2	140 ± 17	0.41 ± 0.05
	2.0	0.12 ± 0.02	0.23 ± 0.03	2.33 ± 0.97	2.48 ± 0.47	2.42 ± 0.13	94.4 ± 15.7	73 ± 5.2	69.4 ± 14.6	141 ± 10	0.49 ± 0.08
	1.0 + P	0.13 ± 0.02	0.24 ± 0.02	2.38 ± 0.67	2.53 ± 0.47	2.79 ± 0.24	83.2 ± 9.6	67 ± 6.9	55.7 ± 11.6	130 ± 16	0.43 ± 0.10
CAZ	0.5	0.14 ± 0.01	0.22 ± 0.02	1.05 ± 0.18	1.97 ± 0.33	2.01 ± 0.16	144 ± 16	66 ± 2.8	75.1 ± 11.6	131 ± 24	0.58 ± 0.09
	1.0	0.13 ± 0.02	0.21 ± 0.02	1.48 ± 0.53	2.18 ± 0.33	1.87 ± 0.15	116 ± 18	75 ± 3.3	87.6 ± 16.1	143 ± 24	0.61 ± 0.05
	2.0	0.14 ± 0.01	0.25 ± 0.02	1.78 ± 0.65	2.37 ± 0.65	1.96 ± 0.18	133 ± 20	60 ± 9.1	81.1 ± 17.6	121 ± 12	0.67 ± 0.12
	1.0 + P	0.13 ± 0.01	0.21 ± 0.01	1.32 ± 0.20	2.23 ± 0.35	1.97 ± 0.17	114 ± 13	68 ± 4.2	78.6 ± 9.4	133 ± 44	0.64 ± 0.19

[a] Data are mean values ± standard deviations of six volunteers. Parameters for CTX were derived from a two-compartment model fitted to serum data of the first 6 h only, whereas for MOX and CAZ all measured data were included. Abbreviations: V_1, volume of distribution of the central compartment; V_D, total volume of distribution; k_{12} and k_{21}, rate constants of transfer between the two compartments; $t_{1/2}$, terminal half-life; Cl_B, total body clearance; *feU*, excreted urinary fraction of the administered dose; Cl_R, renal clearance; Cl_{CR}, creatinine clearance.

[b] P, Probenecid (0.5 g every 6 h on the day before the study and 1.0 g 30 min before the drug was given).

and CAZ were consistently higher than those after 2.0-g doses of CTX. At 8 and 12 h mean CTX concentrations were generally below 0.5 μg/ml, whereas those of CAZ and MOX were approximately 5 to 10 times higher.

The influence of probenecid on the serum kinetics of the three compounds is demonstrated in Fig. 2, which shows the mean concentration time curves from the 1.0-g doses with and without administration of probenecid. The saturation of tubular secretory mechanisms with probenecid considerably decreased the elimination rate of CTX, whereas that of MOX was moderately affected. Probenecid appeared to have no influence on the serum concentrations of CAZ.

The dose response analyzed by AUC versus dose of CTX, MOX, and CAZ is shown in Fig. 3. To facilitate the comparison between the various doses and drugs, the AUCs were normalized. Compared with CTX the normalized AUC of MOX was 3 to 4 times higher, and that of CAZ was 2 to 3 times higher. By intra-individual comparisons the AUC of MOX was 44% larger than that of CAZ. Probenecid increased the AUC of the 1.0 g dose of CTX about twofold, but did not affect that of MOX and CAZ significantly. The mean difference between the AUCs of MOX and CAZ determined with and without administration of probenecid did not exceed 4%.

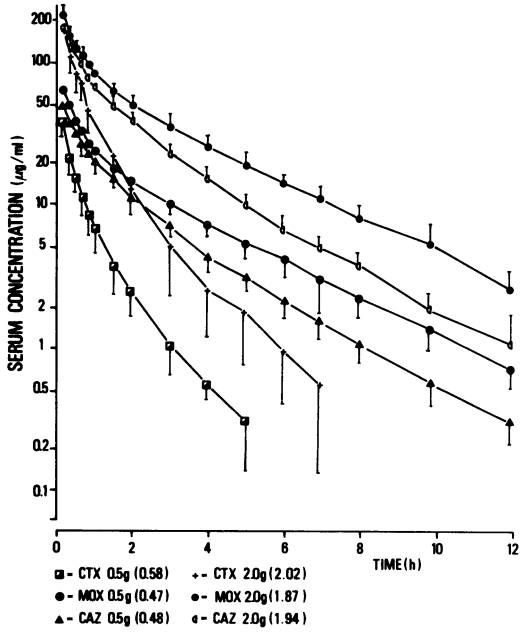

FIG. 1. *Mean serum concentrations and standard deviations of 0.5- and 2.0-g doses of CTX, MOX, and CAZ in six volunteers. The exact amount of antibiotic administered to each volunteer was averaged for the six doses and is included in parentheses.*

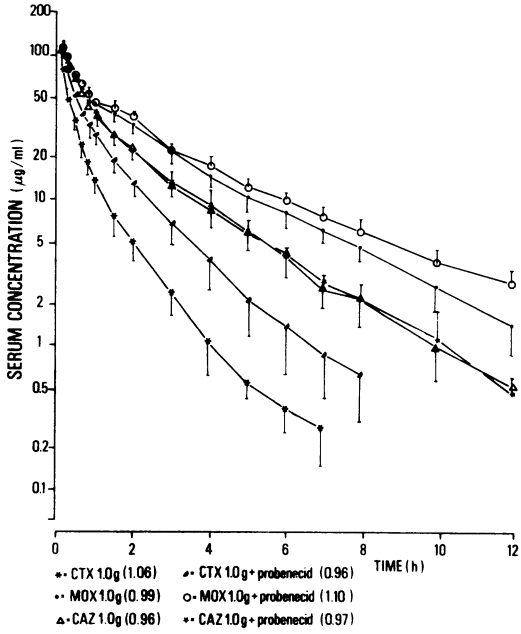

FIG. 2. *Mean serum concentrations and standard deviations of CTX, MOX, and CAZ in six volunteers after a dose of 1.0 g with and without administration of probenecid (0.5 g every 6 h on the day before the study and 1.0 g 30 min before the drug was given). The exact amount of antibiotic administered to each volunteer was averaged for the six doses and is included in parentheses.*

With increasing doses a significant nonlinear increase in AUC was observed for CTX, but not for MOX and CAZ. This could be demonstrated both by an intra-individual comparison of the respective areas and by linear regression analysis of the dose (x in grams) versus normalized AUC (y in microgram·hour per milliliter). This regression yielded a slope for CTX ($y = 13.14x + 45.12$) which was significantly different from zero ($P < 0.001$). This was not the case for the slopes of MOX ($y = -19.36x + 240.09$) and CAZ ($y = -14.59x + 168.51$) (Fig. 3).

Pharmacokinetic parameters. In contrast to MOX and CAZ, several serum concentration time curves of CTX did not exhibit a biexponential decline, suggesting that a two-compartment pharmacokinetic model would not describe all experimental data sets adequately. This phenomenon occurred independently of the administered dose, was observed in all volunteers at least for one dose, and, with the exception of the 1.0-g dose of one volunteer (Fig. 4), could not unambiguously be identified as a triexponential decline. This figure is an example of the unusual pharmacokinetic behavior of CTX and serves to illustrate the problem of correctly defining the elimination half-life. A two-compartment model was applied to fit the data of the 2.0- and 1.0-g doses. No systematic deviations between observed and predicted data points were seen for the 2.0-g dose. This is in contrast to the 1.0-g dose, where serum concentrations were initially fitted in the time period between 0 and 6 h and subsequently fitted between 0 and 10 h (Fig. 4). Inclusion of the 7-, 8-, and 10-h data points into the computer fit prolonged the half-life from 1 h to over 3 h. The problem of defining a realistic half life is summarized in Fig. 5. All individual curves were fitted three times: once by incorporating the data of the first 5 h only, a second time by additionally including the 6-h values, and a third time by incorporating all data for the time periods of 7, 8, 10, or 12 h depending on the number of available measurements above the sensitivity limit of the assay. Figure 5 clearly demonstrates that the half-life of CTX was prolonged as the time period of the computer-fitted data points was increased.

With this nonlinear behavior of CTX (Fig. 3 and 5) the question arises of whether an acceptable quantification results from linear analysis. When a two-compartment open model was fitted to CTX serum data of the first 6 h only, the relative differences between measured and cal-

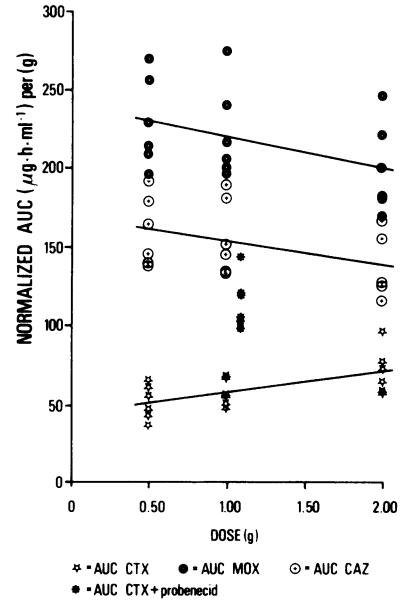

FIG. 3. *Linear regression analysis of the dose response (dose versus normalized AUC) for 0.5-, 1.0-, and 2.0-g doses of CTX, MOX, and CAZ. Data of probenecid studies are not included in regression analyses and are shown for CTX only (for better identification, they are slightly shifted to the right of the data from the 1.0-g dose).*

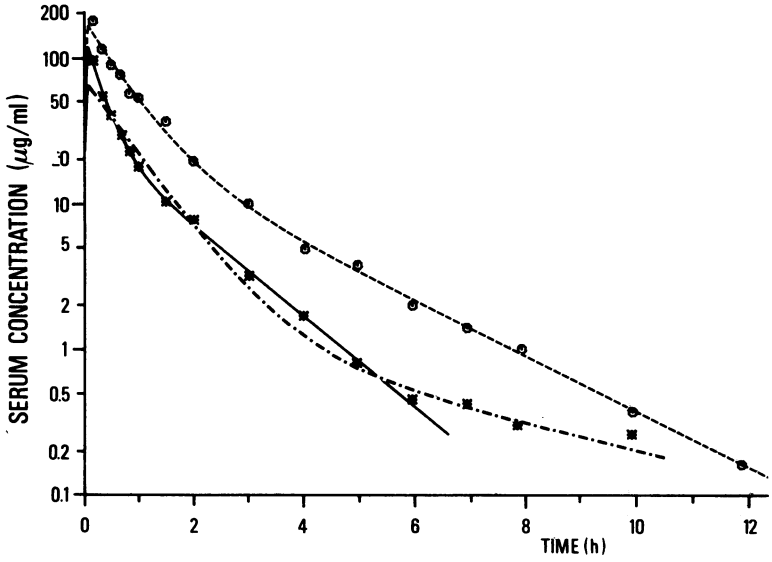

FIG. 4. *CTX serum concentrations of one volunteer demonstrating a biexponential (2.0-g dose) and a triexponential (1.0-g dose) decline. Two-compartment model analysis for data from the 2.0-g dose (-----) and two-compartment model analysis for data between 0 and 6 h (——) and between 0 and 10 h (-·-·-) from the 1.0-g dose.*

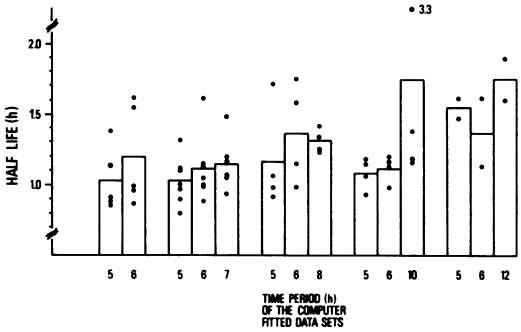

FIG. 5. *Increase of CTX half-life (mean and individual data) in relation to the time periods (5, 6, 7, 8, 10, and 12 h) of the data sets analyzed by a two-compartment model.*

culated concentrations averaged 6.7%. For MOX and CAZ the analysis of the residuals of all measured serum data revealed a mean of 5.4%. Therefore, it may be assumed that for a 6-h period CTX serum kinetics are adequately described by this linear model.

A synopsis of the relevant pharmacokinetic parameters of CTX, MOX, and CAZ is presented in Table 1. Significant differences between the three compounds in the total volume of distribution were observed for the 0.5-g dose (CTX > CAZ > MOX), but not for the 1.0- and 2.0-g dose. Administration of probenecid reversed the order (MOX > CAZ > CTX) by decreasing significantly the volume of distribution of CTX while increasing that of MOX. A significant decrease in the volume of distribution was observed between the 0.5- and 2.0-g dose of CTX, but no dose-dependent changes were recorded for MOX and CAZ. Intra-individual comparisons of the elimination half-lives demonstrated significant differences between each antibiotic. Mean half-lives of the three doses combined were 2.34, 1.95, and 1.16 h for MOX, CAZ, and CTX, respectively. Probenecid increased significantly the half-life of MOX. This observation was seen in only four of six volunteers given CTX and in none given CAZ.

Clearance and urinary excretion. The cumulative urinary recoveries of CTX, MOX, and CAZ are shown in Fig. 6. With one exception (the 0.5-g dose versus the 1.0-g dose of CAZ) no significant differences were recorded between the various doses of each individual drug. It appeared therefore justified to calculate a mean urinary recovery which averaged 53, 75, and 68% of the administered doses for CTX, MOX, and CAZ, respectively. Significant differences in the urinary excretion were observed between CTX and MOX (0.5-, 1.0-, and 1.0-g doses plus probenecid), between CTX and CAZ (1.0- and 1.0-g doses plus probenecid), and between MOX and CAZ (0.5-g dose).

Total body and renal clearance of CTX decreased significantly with increasing doses, and probenecid decreased both clearances almost twofold. Neither phenomenon was observed with MOX and CAZ (Table 1). A comparison between the clearances of the three compounds

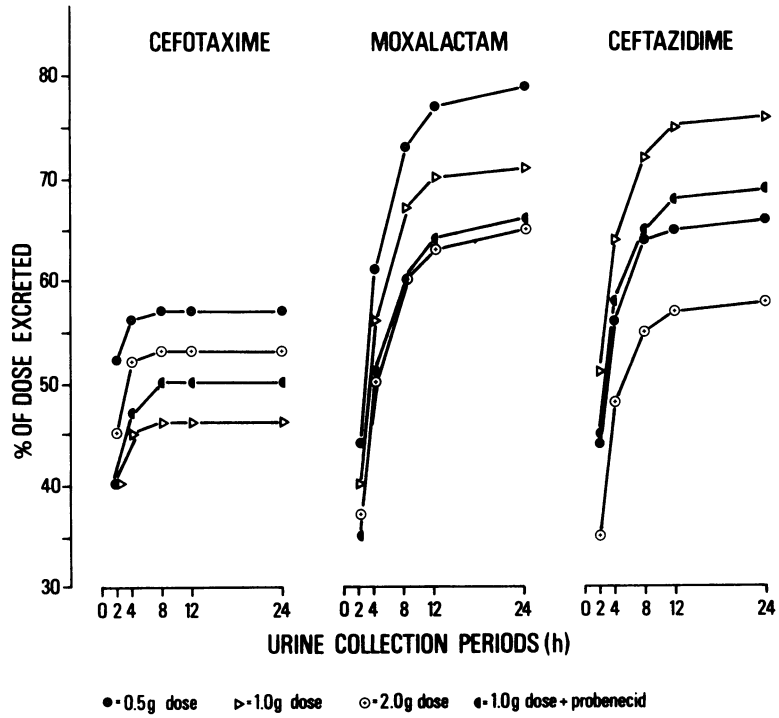

FIG. 6. *Mean cumulative urinary recovery of CTX, MOX, and CAZ in six volunteers.*

revealed a significant decrease from CTX to CAZ to MOX. In contrast to MOX and CAZ the ratio of renal to creatinine clearance indicated considerable tubular secretion for CTX (Table 1). Compared with probenecid data, the proportion of this route of elimination decreased from 60 to 40 to 33% of renal clearance as the dose was increased from 0.5 to 1.0 to 2.0 g.

Serum kinetics of moxalactam epimers determined by HPLC. Freshly prepared solutions of MOX contain two epimers, designated R(−) and S(−), in approximately equal amounts. The serum protein binding of the R(−) epimer averages 53%, and that of the S(−) epimer averages 67% (17). The antimicrobial activity of R(−) is approximately doubled compared with that of S(−) (15). HPLC allows differentiation between the two epimers (15). Figure 7 shows the mean ratio of the concentrations of R(−) and S(−) after intravenous administration of 2.0 and 0.5 g of MOX. The R/S ratio of 0.84 10 min after injection fell to 0.5 at 5 h (2.0-g dose), indicating the presence of twice as much of the S(−) epimer compared with R(−). The decline of the mean ratio for the 0.5-g dose was similar but less uniform.

Serum kinetics of CTX and DES-CTX determined by HPLC. Desacetylation of CTX occurred rapidly in vivo (Fig. 8). After the 0.5- and 2.0-g doses, DES-CTX activity reached its

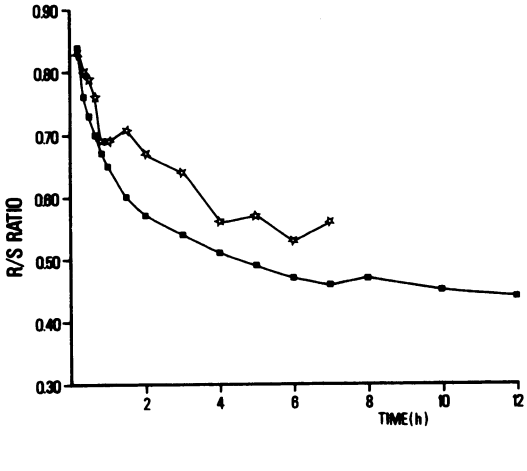

FIG. 7. *Mean ratio of R(−) to S(−) epimers of MOX after intravenous administration of 0.5- and 2.0-g doses to six volunteers (HPLC assay).*

peak after 45 min (Table 2). It declined with a half-life which was approximately twice as long as that of the original compound. Accurate estimates of individual AUCs were difficult to obtain because the sensitivity limit of the HPLC assay method is ≧1.0 μg/ml. Therefore, only a few data points were available to define the half-

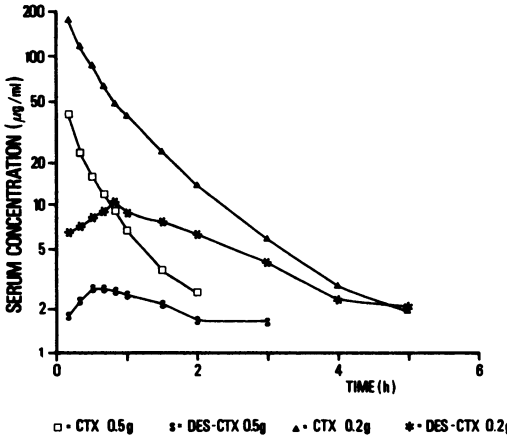

FIG. 8. *Mean CTX and DES-CTX concentrations in six volunteers after doses of 0.5 and 2.0 g of CTX (HPLC assay).*

TABLE 2. *Pharmacokinetic parameters of CTX and DES-CTX in six volunteers after administration of 0.5- and 2.0-g doses (HPLC assay)*[a]

Drug	Dose (g)	Normalized AUC[b]	$t_{1/2}$ (h)[c]	T_{max} (h)[d]	C_{max} (μg/ml)
CTX	0.5	52 ± 16	0.72 ± 0.30	0.17	40.8 ± 9.7
DES-CTX		17 ± 11	1.87 ± 0.70	0.77 ± 0.15	2.7 ± 1.0
CTX	2.0	80 ± 21	0.85 ± 0.27	0.17	176 ± 44.4
DES-CTX		14 ± 4	1.42 ± 0.37	0.78 ± 0.25	9.8 ± 1.8

[a] Data are the means ± standard deviations.
[b] AUC per dose in microgram·hour per milliliter per gram of dose.
[c] Half-life was calculated by linear regression analysis of 3 to 5 terminal concentration time points.
[d] T_{max}, Mean time to reach the mean maximum concentration (C_{max}).

life which is necessary to calculate the terminal portion of the AUC. Nevertheless, the data obtained with the HPLC and agar diffusion method agreed reasonably well (Table 2 and Fig. 3). After the 2.0-g dose the AUC for the desacetyl metabolite was 18 ± 2% of the total area of CTX; for the 0.5-g dose this proportion increased to 31 ± 12%, suggesting that desacetylation may not follow first-order kinetics.

Comparison of the HPLC and the agar diffusion method. The serum concentrations of CTX and MOX (0.5- and 2.0-g doses) which were measured by both microbiological and HPLC assay were compared. The correlation coefficients for the two methods were 0.978 for CTX and 0.955 for MOX. Despite this excellent agreement, a significant difference between bioassay and HPLC results of MOX was observed (paired *t*-test: $P < 0.001$). As Fig. 9 shows, serum concentrations of MOX measured by the agar diffusion method were systematically lower than values obtained with HPLC analysis. The relative difference increased progressively during the first 2 h and remained constant thereafter (mean difference, −26%). This is probably due to the increasing proportion of the S(−) epimer of MOX (Fig. 7) which is microbiologically less active than the R(−) epimer.

No side effects were recorded throughout the entire study, and chemistry profiles, blood counts, urinalysis, and creatinine clearances remained within normal limits.

DISCUSSION

Several published studies have defined the pharmacokinetic properties of CTX, MOX, and CAZ in human volunteers (2, 6, 8, 9, 12, 13). However, they were usually limited to one drug and dose level. Comparisons among the three drugs were difficult since different assay methods were used, and the time periods of administration varied considerably. Therefore, the present study was conducted to evaluate the pharmacokinetics of these compounds in a way which permitted intra-individual comparisons. The same doses which have been proposed for the ongoing clinical trials were used, and the serum concentrations were compared over the usual dosage intervals of 6, 8, and 12 h.

MOX achieved the highest serum concentrations at all dose levels and throughout the entire

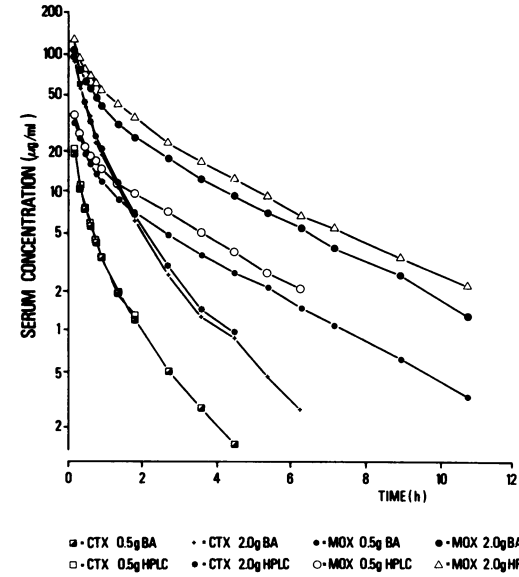

FIG. 9. *Comparison of microbiological assay (BA) and HPLC: mean concentration time curves of six volunteers for 0.5- and 2.0-g doses of CTX and MOX.*

observation period. Compared with MOX, levels of CAZ were only slightly lower, but considerably above those of CTX (Fig. 1 and 2). Despite the difficulties of making an exact comparison, no relevant differences between our study and the results published in the literature were observed (2, 8, 9, 12, 13; S. M. Harding et al., Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 93, 1980).

The half-lives of MOX and CAZ are in the same order of magnitude and approximately twice as long as that of CTX. However, it should be pointed out that the half life of CTX was determined from serum concentration data of the first 6 h only. The definition of the half life is even more complex when it is considered from the viewpoint of antimicrobial activity rather than pharmacokinetic analysis. The desacetyl metabolite of CTX possesses considerable antimicrobial activity, albeit less than that of the original compound (14), and exhibits a half-life which is approximately twice as long as that of CTX. From a therapeutic standpoint it appears reasonable, therefore, to assume that the combined CTX and DES-CTX activity would ensure adequate antimicrobial therapy over a longer period than suggested by the short half-life of approximately 1 h. Nevertheless, if the therapeutic concept is maintained that serum concentrations of an antibiotic should exceed the minimal inhibitory concentration of the majority of the offending pathogens over a period which approximates the entire dosage interval, then MOX and possibly CAZ would appear to be suitable drugs for a twice-daily administration, whereas CTX should probably be administered three or even four times daily.

Despite significant differences in the intraindividual volumes of distribution of CTX, MOX, and CAZ, the values obtained in our study are between 20 and 25% of the body weight comparable to values for most cephalosporins which bind to a similar degree to serum protein (6, 8, 12).

The dose response analyzed by AUC and total body and renal clearance versus dose showed that with increasing doses of CTX the AUC rose in a nonlinear fashion while clearance decreased. The same phenomenon was observed previously in a study in which the pharmacokinetics of CTX were analyzed during steady-state infusions at three different dose levels (6). A saturation of the tubular secretory mechanisms which would become operative with sustaining infusions of 1.0 and 2.0 g per h was then postulated. The assumption of tubular secretion of CTX was confirmed by administration of probenecid in the present study. It became evident that even with the recommended doses of 0.5 to 2.0 g an increasing saturation of tubular secretion can be observed. This would suggest that doses of 0.5 g of CTX are less economical from a pharmacokinetic standpoint than 1- or even 2-g doses. This non-linearity of the dose response was not observed with the other two compounds.

The influence of probenecid on serum concentration, half-life, AUC, volume of distribution, and clearance was most obvious with CTX. Saturation of tubular secretion led to serum concentrations with the 1.0-g dose of CTX which as early as 2 h were higher than those achieved with a 2.0-g dose without probenecid. Similarly, the renal clearance of this drug was decreased by almost 50% and the AUC doubled when probenecid was administered. Therefore, considerable savings could be gained with concomitant administration of probenecid. This is again in contrast to MOX and CAZ, for which the influence of this agent is of no practical significance.

Compared with that of other β-lactam antibiotics, urinary recovery of CTX was unusually low. This may be explained by the fact that the assay strain used in our study measured the original compound only. However, Fu et al. have demonstrated the presence of the desacetyl metabolite of CTX in urine by HPLC (2). Even though the latter is considerably less active in vitro than the parent compound it can be assumed that urinary concentrations of CTX and DES-CTX are sufficient to treat urinary tract infections caused by even moderately susceptible pathogens (10, 14).

The determination of serum levels of MOX and CTX by HPLC provided an opportunity to study the pharmacokinetics of DES-CTX and the behavior of the two epimers of MOX. The metabolism of CTX which occurs in vivo probably accounts at least in part for the frequently and randomly observed deviations from a two-compartment model of behavior. It appears that this metabolism cannot be described adequately by a first-order process. This is demonstrated by the relative difference in AUCs of DES-CTX for the 0.5- and 2.0-g doses. Furthermore, simultaneous simulation of the serum kinetics of CTX and its metabolite with a pharmacokinetic model which incorporated first-order desacetylation did not result in satisfactory fits of the two concentration time curves (unpublished observations). Additional studies are necessary to define the extent and rate of desacetylation to avoid accumulation of DES-CTX in patients with renal disease (10).

At present it is difficult to speculate on the clinical relevance of differentiating between the

two epimers of MOX. This study showed that there was a systematic difference between results obtained with bioassay and HPLC procedures. This difference increased as the R/S ratio decreased from an initial value of 0.84 to 0.5 at approximately 4 h after injection, when the concentration of the S(−) epimer, which has approximately 50% of the antimicrobial activity of the R(−) epimer, was doubled (15). Consequently, the activity of MOX, measured by bioassay, was reduced by one-fourth compared with results obtained by HPLC analysis.

The comparison between the two assay methods, performed blindly in two different locations, documents a very satisfactory interlaboratory agreement. The precision of the agar diffusion method, expressed as the mean coefficient of variation determined from 165 spiked serum and phosphate-buffered saline samples, was 4.6 ± 0.9%. It was fairly constant over the entire range of concentrations and did not show significant differences among the three antibiotics. The excellent agreement for the two assay methods of CTX is illustrated in Fig. 9, which documents that the *P. morganii* strain virtually measures intact CTX only.

CTX, MOX, and CAZ are three new semisynthetic cephalosporins with extraordinary activity against gram-negative organisms. Despite quantitative differences, their in vitro performance is comparable. However, we demonstrated significant differences in their pharmacokinetic behavior. The term "favorable pharmacokinetics" has been applied to a variety of new antimicrobial agents. If it has any clinical relevance in the treatment of patients, MOX and CAZ would probably qualify for such a label due to their long half-lives. It will be interesting to compare the clinical efficacy of these two compounds with favorable pharmacokinetics versus one with less favorable pharmacokinetics.

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