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

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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-ceftaxime 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 subsequently 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 mirabilis 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. mirabilis 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.

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 (V1), rate constants of transfer between the two compartments (k12 and k21), and rate constant of elimination (k4) were adapted to the experimental data with a nonlinear fitting program by minimizing the sum of weighted squared deviations (?). 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 (t1/2) was then defined by these parameters. The total volume of distribution (Vd), total body clearance (Clb), and total renal clearance (Cler) were calculated by the following equations: Vd = V1 (1 + k12/k21), Clb = V1k4, and Cler = Clb - 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 drugs and doses, AUCs were normalized by dividing through the individual doses. For all statistical evaluations the Wilcoxon matched-pairs signed rank test was used. Probabilities of 2α ≤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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (g)</th>
<th>V₁ (liters/kg)</th>
<th>V₀ (liters/kg)</th>
<th>k₁₂ (10⁻⁴/h)</th>
<th>k₁₃ (10⁻⁴/h)</th>
<th>t₁/₂ (h)</th>
<th>C₁₀ (ml/min)</th>
<th>fₑU (%)</th>
<th>C₀ (ml/min)</th>
<th>C₀/C₂ (ml/min)</th>
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<tbody>
<tr>
<td>CTX</td>
<td>0.5</td>
<td>0.17 ± 0.04</td>
<td>0.29 ± 0.05</td>
<td>2.30 ± 1.10</td>
<td>3.05 ± 1.12</td>
<td>1.10 ± 0.38</td>
<td>391 ± 97</td>
<td>58 ± 12</td>
<td>217 ± 31</td>
<td>129 ± 18</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>0.14 ± 0.03</td>
<td>0.24 ± 0.04</td>
<td>2.10 ± 0.72</td>
<td>2.96 ± 0.85</td>
<td>1.08 ± 0.27</td>
<td>326 ± 48</td>
<td>47 ± 7.9</td>
<td>154 ± 38</td>
<td>132 ± 16</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>0.15 ± 0.02</td>
<td>0.21 ± 0.04</td>
<td>1.00 ± 0.43</td>
<td>2.13 ± 0.73</td>
<td>1.31 ± 0.32</td>
<td>267 ± 49</td>
<td>56 ± 18</td>
<td>145 ± 46</td>
<td>141 ± 18</td>
</tr>
<tr>
<td></td>
<td>1.0 + P³</td>
<td>0.10 ± 0.01</td>
<td>0.18 ± 0.02</td>
<td>3.40 ± 0.82</td>
<td>3.97 ± 0.55</td>
<td>1.15 ± 0.03</td>
<td>169 ± 16</td>
<td>51 ± 3.6</td>
<td>85 ± 8.8</td>
<td>124 ± 10</td>
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<td>MOX</td>
<td>0.5</td>
<td>0.09 ± 0.01</td>
<td>0.18 ± 0.01</td>
<td>2.45 ± 0.60</td>
<td>2.63 ± 0.73</td>
<td>2.35 ± 0.32</td>
<td>77.8 ± 9.4</td>
<td>79 ± 4.8</td>
<td>61.7 ± 9.0</td>
<td>135 ± 18</td>
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<tr>
<td></td>
<td>1.0</td>
<td>0.10 ± 0.01</td>
<td>0.19 ± 0.01</td>
<td>3.35 ± 1.18</td>
<td>3.47 ± 1.03</td>
<td>2.25 ± 0.21</td>
<td>81.2 ± 10.6</td>
<td>71 ± 7.3</td>
<td>58.0 ± 9.2</td>
<td>140 ± 17</td>
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<tr>
<td></td>
<td>2.0</td>
<td>0.12 ± 0.02</td>
<td>0.23 ± 0.03</td>
<td>2.33 ± 0.97</td>
<td>2.48 ± 0.47</td>
<td>2.42 ± 0.13</td>
<td>94.4 ± 15.7</td>
<td>73 ± 5.2</td>
<td>69.4 ± 14.6</td>
<td>141 ± 10</td>
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<td></td>
<td>1.0 + P³</td>
<td>0.13 ± 0.02</td>
<td>0.24 ± 0.07</td>
<td>2.38 ± 0.67</td>
<td>2.53 ± 0.47</td>
<td>2.79 ± 0.24</td>
<td>83.2 ± 9.6</td>
<td>67 ± 0.9</td>
<td>55.7 ± 11.5</td>
<td>130 ± 16</td>
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<td>CAZ</td>
<td>0.5</td>
<td>0.14 ± 0.01</td>
<td>0.22 ± 0.02</td>
<td>1.05 ± 0.58</td>
<td>1.97 ± 0.33</td>
<td>2.01 ± 0.16</td>
<td>144 ± 16</td>
<td>66 ± 2.8</td>
<td>75.1 ± 11.6</td>
<td>131 ± 24</td>
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<tr>
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<td>1.0</td>
<td>0.13 ± 0.02</td>
<td>0.21 ± 0.02</td>
<td>1.48 ± 0.53</td>
<td>2.18 ± 0.33</td>
<td>1.87 ± 0.15</td>
<td>116 ± 18</td>
<td>75 ± 3.3</td>
<td>87.6 ± 16.1</td>
<td>143 ± 24</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>0.14 ± 0.01</td>
<td>0.25 ± 0.02</td>
<td>1.78 ± 0.65</td>
<td>2.37 ± 0.65</td>
<td>1.96 ± 0.18</td>
<td>133 ± 20</td>
<td>60 ± 9.1</td>
<td>81.1 ± 17.5</td>
<td>121 ± 12</td>
</tr>
<tr>
<td></td>
<td>1.0 + P³</td>
<td>0.13 ± 0.01</td>
<td>0.21 ± 0.01</td>
<td>1.32 ± 0.20</td>
<td>2.23 ± 0.35</td>
<td>1.97 ± 0.17</td>
<td>114 ± 13</td>
<td>68 ± 4.2</td>
<td>78.6 ± 9.4</td>
<td>133 ± 44</td>
</tr>
</tbody>
</table>

* 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: V₁, volume of distribution of the central compartment; V₀, total volume of distribution; k₁₂ and k₁₃, rate constants of transfer between the two compartments; t₁/₂, terminal half-life; C₁₀, total body clearance; fₑU, excreted urinary fraction of the administered dose; C₀, renal clearance; C₀/C₂, creatinine clearance.

³ 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).
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. 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.
versed the order of CTX distribution decreasing significantly were observed for MOX, CAZ, and CTX, respectively. Probencid 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...
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 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-
bioassay and HPLC results agreement, and the coefficients were 0.978 for the diffusion method.

After 3 h, the concentrations agreed with the HPLC assay. Nevertheless, the 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 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,
observation period. Compared with MOX, levels of CAZ were only slightly lower, but consider-
ably 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.,
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 anti-
microbial 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 com-
bined 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 therapeu-
tic concept is maintained that serum concen-
trations of an antibiotic should exceed the min-
imal 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
tree or even four times daily.

Despite significant differences in the intrain-
dividual volumes of distribution of CTX, MOX,
and CAZ, the values obtained in our study are
between 20 and 25% of the body weight compara-
table 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 infu-
sions at three different dose levels (6). A satu-
ration of the tubular secretory mechanisms
which would become operative with sustaining
infusions of 1.0 and 2.0 g per h was then postu-
lated. The assumption of tubular secretion of
CTX was confirmed by administration of pro-
benecid 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 secre-
tion 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 concen-
tration, half-life, AUC, volume of distribution,
and clearance was most obvious with CTX. Sat-
uration of tubular secretion led to serum concen-
trations 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, consid-
erable savings could be gained with concomitant
administration of probenecid. This is again in
contrast to MOX and CAZ, for which the influ-
ence of this agent is of no practical significance.

Compared with that of other β-lactam anti-
biotics, 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 as-
sumed that urinary concentrations of CTX and
DES-CTX are sufficient to treat urinary tract
infections caused by even moderately suscepti-
ble 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 prob-
ably 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, simulta-
neous simulation of the serum kinetics of CTX
and its metabolite with a pharmacokinetic model
which incorporated first-order desacety-
lation did not result in satisfactory fits of the
two concentration time curves (unpublished ob-
servations). 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

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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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