Pharmacokinetics of Cefotaxime

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The pharmacokinetics of cefotaxime after intramuscular injection and intravenous infusion were determined. The mean peak serum level after the 500-mg intramuscular dose was 11.7 μg/ml, and it was 20.5 μg/ml after a 1,000-mg dose. The serum half-life was 1.2 and 1.3 h, respectively for the two doses. The apparent fractional volumes of distribution of 32 and 37 liters were not significantly different for the two doses, and the fractional serum clearance was approximately 315 ml/min per 1.73 m² for both doses. The mean peak serum level after 1,000 mg administered by intravenous infusion over 30 min was 41.1 μg/ml. The half-life was 1.13 h, apparent volume of distribution was 33 liters, serum clearance 341 ml/min per 1.73 m², and renal clearance was 130 ml/min per 1.73 m². The pharmacology of cefotaxime is similar to the pharmacology of other cephalosporin antibiotics, but the low inhibitory levels which it has against gram-positive and gram-negative bacteria suggest that lower dosage regimens should be possible.

Cefotaxime is a new cephalosporin with an extremely broad range of antibacterial activity (5). It has been shown in vitro to inhibit not only most clinically significant gram-positive cocci and the members of the Enterobacteriaceae, but also many Bacteroides fragilis and Pseudomonas aeruginosa (4, 8). Furthermore, cefotaxime inhibits most Escherichia coli, Klebsiella pneumoniae, and Proteus at concentrations below 1 μg/ml. The purpose of this study was to determine the pharmacokinetic parameters of cefotaxime after intravenous and intramuscular administration to normal volunteers.

MATERIALS AND METHODS

Cefotaxime was supplied by Hoechst-Roussel Pharmaceuticals, Inc. as a sodium salt in vials containing 500 or 1,000 mg. Twenty-four male volunteers between 21 and 33 years of age were the subjects used in this study. Informed consent in accordance with federal guidelines was obtained. The mean weight of the subjects was 78.25 (±3.69) kg. The mean age was 26.4 years, and the mean body surface area was 1.96 m². All subjects were judged healthy on the basis of history, physical examinations, chemistry profile (SMA 12/60, Technicon), complete blood count, urinalysis, and creatinine clearance. Subjects with known sensitivity to penicillins or cephalosporins were excluded.

Intramuscular injection study. Fourteen subjects were divided into two groups. Group A (seven subjects) received an intramuscular injection of 500 mg of cefotaxime, followed 1 week later by a 1,000-mg injection. Group B (seven subjects) received 1,000 mg followed 1 week later by a 500-mg dose. Blood samples were obtained at 0, 15, 30, 45, 60, 90, 120, 180, 240, and 360 min after the injection. Urine samples were collected immediately before injection and at 0 to 2, 2 to 4, 4 to 6, 6 to 12, and 12 to 24 h after the drug had been administered. Blood samples were allowed to clot at room temperature and centrifuged, and the serum was decanted within 1 h of collection. Each serum and urine sample was divided in aliquots, immediately frozen, and stored at −20°C until assay. Cefotaxime in urine, serum, and phosphate buffer was found to be stable for 3 months at −20°C at concentrations of 50 μg/ml.

Intravenous infusion study. Ten healthy males were selected for this study. Each received 1,000 mg of cefotaxime infused intravenously through a small-bore needle over a 30-min period. Blood samples were drawn before infusion and at 30, 45, 60, 75, 90, 120, 180, and 240 min after the start of the infusion. Urine samples were collected before infusion of the agent and at intervals of 0 to 2, 2 to 4, 4 to 6, and 12 to 24 h. Samples were processed as detailed above.

Assays. Cefotaxime was assayed by the agar well diffusion technique, using antibiotic medium no. 2 (Difco Laboratories) as previously described (2, 7) and in glass plates (14 by 14 inches [ca. 35.56 cm²]). Cefotaxime was dissolved in potassium phosphate buffer, (pH 7.0; 0.05 M). Antibiotic standards for assay of serum samples were prepared in pooled normal human serum which had no antibacterial activity. Standards for urine samples were prepared in the buffer. Concentrations of ≥0.16 μg of cefotaxime per ml could be detected with the assay organism E. coli 3989 from our collection. Serum and urine samples were assayed in quadruplicate. The assay organism was 80-fold less susceptible to desacetylcefotaxime.

Biogram of cefotaxime. A solvent system of isopropanol-pyridine-water (65:5:30, vol/vol) was used to detect defoxatime and desacylated cefotaxime. Stan...
dard cefotaxime, deacetylated cefotaxime, and urine samples from patients were applied to Whatman no. 1 paper (Reeve Angel), which was subjected to overnight descending development in the solvent system. Paper chromatograms were briefly air dried and placed on agar plate prepared with antibiotic medium no. 2 (Difco) which had been inoculated with Bacillus subtilis spores. After 15 min of contact, the paper was removed and the plate was incubated overnight at 37°C. The migration of the two compounds in urine was sufficiently different to separate them when assayed from patients or in urine to which the compounds were added.

**Pharmacokinetic and statistical methods.** A one-compartment, open model was used to calculate the pharmacokinetic parameters of cefotaxime after intramuscular administration (10). The mathematical model was 

\[ C = (A_0 K_a / K_e) (e^{-K_e t} - e^{-K_a t}) \]

where \( C \) is the serum concentration at time \( t \), \( K_a \) is the absorption rate constant, \( K_e \) is the elimination rate constant, and \( A_0 \) is equal to \( F X_0 / V \) (where \( F \) is the fraction of dose, \( X_0 \) is the dose, and \( V \) is the volume of distribution). The parameters \( A_0 \), \( K_a \), and \( K_e \) were estimated from the curves fitted to the experimental data by the least-squares method. The inverse of the squared observed value was used as the weight for the nonlinear iteration process. The computer program NONLIN (6) was used in the computation. The fractional apparent volume of distribution \( V/F \) was calculated by

\[ V/F = (\text{dose}/A_0) \times 1.73/\text{BSA}. \]

The serum and renal clearances were determined by the formulas

\[ C_{\text{f}1}/F = (\text{dose}/AUC_{\text{f}0-\infty}) \times 1.73/\text{BSA} \]

and

\[ C_{\text{f}2}/F = \left( U_{\text{f}0-\infty} - A_0 / K_e \right) \times 1.73/\text{BSA}. \]

BSA is body surface area calculated as weight\(^{0.425} \times \text{height}^{0.726} \times 0.007184. AUC \text{ was area under the curve, calculated as } AUC_{\text{f}0-\infty} = A_0 / K_e. \]

A two-compartment, open model was used to calculate the pharmacokinetics of cefotaxime after intravenous infusion (7, 11). Since cefotaxime was infused over 30 min, an exponential equation, \( C = R e^{-\alpha t} + S e^{-\beta t} \), expressed the serum concentration time curve. The relationships between the coefficients \( R \) and \( S \) and the coefficients \( A \) and \( B \) for this model are:

\[ A = (R T)/(\alpha t - 1) \]

and

\[ B = (S T)/(\beta t - 1) \]

where \( \alpha \) and \( \beta \) are hybrid rate constants and \( T \) is the time when the infusion is stopped. If the duration of infusion, infusion rate, and the coefficients \( A \) and \( B \) are known, the rate constants \( (K_{10}, K_{30}, \text{ and } K_{90}) \), as well as the apparent volume of distribution \( (V_d) \), central compartment \( (V_c) \), peripheral tissue compartment \( (V_d) \), and steady state \( (V_{\text{ss}}) \), during \( \beta \) phase can be calculated. The half-lives are calculated by

\[ T_{1/2} = 0.693/\alpha \]

and

\[ T_{1/2} = 0.693/\beta. \]

Serum and urine clearances were calculated by utilizing the above data adjusted for body surface area. A NONLIN program was used to fit the data and initial estimates for coefficients and exponents were based on the CSTRIP technique (10).

**RESULTS**

**Intramuscular study.** Because subject 14 did not complete the study, 13 subjects were used in the analysis. The mean serum concentrations after 500 and 1,000 mg are shown in Fig. 1. The pharmacokinetic parameters are given in Table 1. The mean peak serum concentration after 500 mg was 11.7 (±0.7) μg/ml. The peak serum concentration was reached within 22 min. The mean peak serum concentration after 1,000 mg/μl was 20.5 (±1.9) μg/ml, but this was reached at 30 min after injection. At the end of 4 hours, the mean serum level after 500 mg was 1.4 (±0.15) μg/ml and 3.6 (±0.36) μg/ml after 1,000 mg. At 6 h after injection of 1,000 mg, the mean serum level still exceeded 1 μg/ml. There was a moderate amount of intrasubject variation in serum concentrations which could not be correlated with weight, body surface area, or creatinine clearance. No statistically significant differences were noted between the two dose groups for the times to peak and the normalized mean peak serum levels. The areas under the curves for the period of 0 to 6 h and 0 to infinity when normalized for dose were essentially identical, with \( AUC_{0-4} = 23.2 \) μg/ml per h for the 500-mg dose and 45.7 μg/ml per h for the 1,000-mg dose.

The mean half-life of cefotaxime after the administration of the 500-mg dose by the intramuscular route was 1.20 h, and it was 1.34 h after the 1,000-mg dose. The absorption rate constant \( K_a \) was 12.89 for the 500-mg dose, compared with 8.68 for the 1,000-mg dose, but the elimination rate constant \( K_e \) was 0.591 for the 500-mg dose and 0.544 for the 1,000-mg dose. Although the apparent volume of distribution for the 500-mg dose was 32.4 liters/1.73 m² compared with 37.2 liters/1.73 m², the difference is not statistically significant. The fractional serum clearances after the 500- and 1,000-mg doses were virtually identical—315 and 318 ml/min per 1.73 m².

Figure 2 shows the excretion of cefotaxime. Approximately one-fifth of the dose was ex-
creted in the first 2 h, with 39% of the 500-mg dose and 33% of the 1,000-mg dose recovered in 24 h. The renal clearance was 122 ml/min per 1.73 m² for the 500-mg dose and 104 ml/min per 1.73 m² for the 1,000-mg dose. These differences are not statistically significant. Urine concentrations in the first 2 h after the dose obviously depended upon volume but ranged from 90 to 3,261 μg/ml for the 500-mg dose and from 151 to 2,178 μg/ml for the 1,000-mg dose.

The low urinary recovery of cefotaxime prompted us to investigate whether a proportion of the compound was converted to the desacetyl derivative. This is indeed the case (Fig. 3) and undoubtedly explains the low recovery of parent compound. We did not assay the percentage of drug converted to the desacetyl derivative. Stud-
lies to determine this are underway with a high performance liquid chromatography method.

**Intravenous study.** The mean serum levels after infusion of 1,000 mg of cefotaxime are shown in Fig. 4. The pharmacokinetic parameters after intravenous infusion are given in Table 2. The mean peak serum concentration occurred at the end of the 30-min infusion and was 41.1 (±11.6) µg/ml. At the end of 4 h, the mean serum level was 1.5 µg/ml. Minor inter-

subject variation in serum levels did not correlate with the differences in body size of the subjects or with the minor differences in creatinine clearance in these normal individuals.

The disposition of cefotaxime during the \( \alpha \) phase lasted approximately 1 h. Rate constants for the \( \alpha \) phase were 2.57 to 4.74 h\(^{-1}\), whereas rate constants for the \( \beta \) phase were 0.49 to 0.71 h\(^{-1}\). The mean \( T^{1/2}_\alpha \) was 13 min and the mean \( T^{1/2}_\beta \) was 68 min. The apparent volume of distribution at steady state, \( V_{ss} \), was 21.64 liters/1.73 m\(^2\), whereas the mean \( V_d \) area, the distribution volume of the \( \beta \) phase, was 33.3 liters/1.73 m\(^2\). The mean serum clearance was 342 ml/min per 1.73 m\(^2\).

The urinary recovery ranged from 22 to 66%, with a mean urinary recovery of 37% of an administered dose (Fig. 5). The majority of uri-

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### Table 2. Pharmacokinetic parameters of cefotaxime administered by intravenous infusion of 1,000 mg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak level</td>
<td>41.1 µg/ml</td>
</tr>
<tr>
<td>Disposition rate constant ( \alpha )</td>
<td>3.43 h(^{-1}) (0.23)</td>
</tr>
<tr>
<td>Disposition rate constant ( \beta )</td>
<td>0.62 h(^{-1}) (0.02)</td>
</tr>
<tr>
<td>( K_{10} )</td>
<td>1.05 h(^{-1}) (0.13)</td>
</tr>
<tr>
<td>( K_{31} )</td>
<td>1.21 h(^{-1}) (0.10)</td>
</tr>
<tr>
<td>( K_{10} )</td>
<td>1.80 h(^{-1}) (0.09)</td>
</tr>
<tr>
<td>( T^{1/2}_\alpha )</td>
<td>0.21 h (0.01)</td>
</tr>
<tr>
<td>( T^{1/2}_\beta )</td>
<td>1.13 h (0.04)</td>
</tr>
<tr>
<td>( V_c )</td>
<td>11.6 liters/1.73 m(^2) (0.90)</td>
</tr>
<tr>
<td>( V_t )</td>
<td>10.1 liters/1.73 m(^2) (1.42)</td>
</tr>
<tr>
<td>( V_{ss} )</td>
<td>21.5 liters/1.73 m(^2) (2.11)</td>
</tr>
<tr>
<td>( V_d ) area</td>
<td>33.3 liters/1.73 m(^2) (3.03)</td>
</tr>
<tr>
<td>( V_d ) ext</td>
<td>60.2 liters/1.73 m(^2) (5.64)</td>
</tr>
<tr>
<td>Serum clearance</td>
<td>341.6 ml/min per 1.73 m(^2) (26.9)</td>
</tr>
<tr>
<td>AUC</td>
<td>44.3 µg/ml per h (3.37)</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>130.1 ml/min per 1.73 m(^2) (17.2)</td>
</tr>
</tbody>
</table>

* Values in parentheses indicate standard error.
nary excretion occurred in the first 2 h after injection. The range of urinary concentration was large, due to variation in the volume of urine produced. The renal clearance was 130 ml/min per 1.73 m². As with intramuscular injection, cefotaxime appeared in the urine as the desacetyl derivative after intravenous injection.

Tolerance. Cefotaxime was well tolerated in both the intramuscular and intravenous studies. There was minimal discomfort, and phlebitis was not encountered. Hematological and chemical parameters were normal after the study.

DISCUSSION

Cefotaxime differs from the commercially available cephalosporins in several aspects. On a microgram per milliliter basis, it is much more active than any other agent against such diverse organisms as S. pneumoniae, H. influenzae, N. Gonorrhoeae, E. coli, K. pneumoniae, and E. cloacae (4, 8). It inhibits these bacteria at concentrations below those needed for aminoglycosides; that is, less than 1 μg/ml. Furthermore, cefotaxime inhibits many strains of B. fragilis and P. aeruginosa (4, 8).

The pharmacokinetic parameters of cefotaxime found in this study show that an intramuscular dose of 500 or 1,000 mg would provide serum and urine levels which would readily inhibit most important gram-positive species and most members of the Enterobacteriaceae. The serum levels achieved after intravenous administration of 1,000 mg over 30 min also would inhibit a significant proportion of B. fragilis and P. aeruginosa. However, in the treatment of infections due to these latter species, higher doses probably would be necessary, and intramuscular therapy of P. aeruginosa infections would be suitable only if the infection were localized to the urinary tract.

It has been necessary to analyze the pharmacokinetic parameters of cephalosporin antibiotics administered intravenously by the two-compartment open model, as several groups have shown, since the short distribution phase may result in an artificially short half-life (1, 3, 9). Although this compound, like cephalothin and cephalin, is converted to a less active desacetyl derivative, the use of an assay organism which is much less susceptible to the derivative than the parent compound indicates that the pharmacokinetic parameters obtained reflect the serum concentration of cefotaxime. Comparisons of the results of assays performed by microbiological and high performance liquid chromatography methods in which one can assay for both components are in preparation.

The pharmacokinetic parameters of cefotaxime are similar in some ways to those reported for cephalothin (1, 3). Both compounds are converted to desacetyl derivatives. The mean peak serum level of cefotaxime of 20 μg/ml for 1 g administered intramuscularly is similar to that for 1 g of cephalin, cefamandole, or cefoxitin. However, 90% of E. coli, K. pneumoniae, and P. mirabilis are inhibited by 0.2 μg of cefotaxime per ml, compared with the levels of 3 to 12 μg/ml which are required for the other agents to inhibit these species (4, 7). Although the T1/2 of cefotaxime is relatively short, similar to that of cephalothin, cefamandole, and cefoxitin, adequate serum concentrations are present for 4 to 6 h after intramuscular or intravenous injection of 500 or 1,000 mg.

These studies show that cefotaxime undergoes rapid distribution in the body. The differences in renal and plasma clearance of cefotaxime probably are related to its conversion to the desacetyl derivative.

On the basis of the low protein binding of cefotaxime (30% [8]), which is lower than that of the older cephalosporins, such as cephalothin and cephapirin, and considerably lower than the 85% protein binding of cefazolin, as well as its known excellent in vitro activity and its killing kinetics shown against both gram-positive and gram-negative species (8), it should be possible to treat respiratory soft tissue and urinary tract infections due to susceptible pathogens with less frequent dosing than has been utilized with the older cephalosporins, such as cephalothin, even though the serum half-lives are similar.

LITERATURE CITED


