Pharmacokinetics of Cefotaxime and Desacetylcefotaxime in Patients with Liver Disease

RICHARD J. KO,1 FRED R. SATTLER,2 SHARON NICHOLS,2 EVANGELOS AKRIVIADIS,2 BRUCE RUNYON,2† MARIA APPLEMAN,2 JORDAN L. COHEN,2‡ AND ROBERT T. KODA1* 

Schools of Pharmacy1 and Medicine,2 University of Southern California, Los Angeles, California 90033

Received 23 October 1990/Accepted 15 April 1991

The dispositions of cefotaxime and its metabolite desacetylcefotaxime were investigated in patients with different forms of chronic parenchymal liver disease (CPLD). A total of 31 subjects (27 patients and 4 controls) received a single 2-g dose of cefotaxime by infusion, and serial blood samples were drawn. The area under the concentration-time curve ranged from 176 to 241 μg · h/ml, the apparent half-life ranged from 1.49 to 2.42 h, and clearance ranged from 2.06 to 3.10 ml/min/kg in patients with four different forms of CPLD. The area under the concentration-time curve and the apparent half-life of desacetylcefotaxime ranged from 72 to 128 μg · h/ml and 7.1 to 13.4 h, respectively. Pharmacokinetic parameters were significantly different in patients with CPLD compared with those in control subjects and were related to clinical indices of hepatic impairment. Modest accumulation of cefotaxime in patients with severe hepatic impairment is unlikely to produce toxicity because of its high therapeutic index, and dosing modifications may not be required.

Cefotaxime (Claforan; Hoechst-Roussel Pharmaceuticals, Inc., Somerville, N.J.), an expanded-spectrum cephalosporin, has a broad spectrum of antibacterial activity against aerobic cocci and enteric gram-negative bacilli. Cefotaxime is normally cleared by both renal excretion and hepatic metabolism and has been extensively studied in both human and animal models (2, 4, 5, 7, 12-14, 17). The major metabolite of cefotaxime, desacetylcefotaxime, also possesses antibacterial activity that is often synergistic with the parent compound. In vivo evidence suggests that the liver is the primary site for the formation of desacetylcefotaxime, although the kidney has also been shown to be capable of this conversion in vitro (7).

The pharmacokinetics of cefotaxime and desacetylcefotaxime have been reported previously in patients with parenchymal liver disease (8-10, 19, 20). However, the relationship of clearance and other pharmacokinetic parameters of cefotaxime and desacetylcefotaxime to specific clinical manifestations of liver disease, such as decreased hepatic function with hypalbuminemia, jaundice, and ascites, has not been established. It is probable that the ratio of cefotaxime and desacetylcefotaxime, and thus, the total bactericidal activity in blood and body fluids, differs in patients with various forms of liver disease. In addition, patients with chronic parenchymal liver disease (CPLD) are prone to serious and even life-threatening infections. Spontaneous bacterial peritonitis is one such complication and is associated with a mortality rates ranging from 30 to 100% (18). The wide range reported may be related more to the variability of the underlying liver disease than to the infection per se. It is important, therefore, to determine whether impaired disposition of cefotaxime and desacetylcefotaxime from blood and ascites differs among patients with various forms of chronic liver disease and thereby predisposes certain patients to a high risk of fatality during spontaneous bacterial peritonitis. To this end, a study was conducted to determine the pharmacokinetics of cefotaxime and desacetylcefotaxime in patients with CPLD and in normal control subjects.

MATERIALS AND METHODS

Subjects. Twenty-seven subjects with CPLD, with or without jaundice, edema, or ascites, were recruited from patients at Rancho Los Amigos Hospital, Downey, Calif. Each patient had to fulfill at least two of the following criteria for inclusion into the study: (i) biopsy-proven cirrhosis, (ii) esophageal varices or abdominal wall collateral veins, (iii) serum ascites albumin gradient of ≥1.1 g/dl (15), or (iv) redistribution of colloid on liver-spleen scan. In addition, four normal subjects served as controls. Subjects were selected to fill four different groups according to their clinical status. Group I (six subjects) consisted of patients with CPLD but without jaundice, edema, or ascites; group II (six subjects) consisted of patients with CPLD and ascites (total bilirubin, <2.0 mg/dl); group III (eight subjects) consisted of patients with CPLD and jaundice (total bilirubin, ≥2.0 mg/dl) but without edema or ascites; and group IV (seven subjects) consisted of patients with CPLD and jaundice and ascites. Group V (four subjects) consisted of normal control subjects.

Exclusion criteria included clinical evidence of bacterial infection (leukocyte count, >15,000/mm3 or >20% band forms), serum creatinine of ≥1.4 mg/dl, concurrent therapy with other antibiotics, history of type I hypersensitivity reactions (hives, angioedema, anaphylaxis), exfoliative dermatitis, or other life-threatening reactions to beta-lactam antibiotics or the inability to comprehend and sign an informed consent.

Procedure and study design. Upon admission to the study, each subject was given a physical examination, blood was collected for chemistry and complete blood count, and
urinalysis was performed. Each subject received a single 2.0-g dose of cefotaxime dissolved in 100 ml of normal saline which was administered via an intravenous cannula through an intravenous controller over a 30-min period. The cannula was flushed with 10 ml of normal saline at the completion of the infusion and before each blood collection. Samples of 5 ml of venous blood were collected preinfusion and at 10, 20, 30, and 45 min and 1.0, 1.25, 1.5, 2.0, 2.5, 3.5, 4.5, 6.5, 8.5, 12.5, 24.5, 30.5, and 48.5 h after the start of the infusion. Serum was separated from clotted venous blood within 2 h of collection. In addition, a 20-ml sample of peritoneal fluid was collected at 6 and 24 h after infusion in the 13 patients with ascites (groups II and IV). Samples were stored at −70°C until they were analyzed for drug concentrations.

Analytical methodology. Cefotaxime (92.5% free acid) and desacetylcefotaxime were supplied by Hoechst-Roussel Pharmaceuticals. Cefotaxime was purchased from Smith Kline & French Laboratories (Philadelphia, Pa.) and served as the internal standard.

High-performance liquid chromatography procedure. To 200 μl of serum containing cefotaxime and desacetylcefotaxime was added 16 μl of internal standard (0.5 mg/ml). The mixture was passed through a solid extraction column (SAX Quaternary amine, 100 mg/1.0 ml; Analytichem International, Harbor City, Calif.) and washed with 0.5 ml of distilled water. The drug and internal standard were eluted from the column with 0.2 M sodium acetate buffer (pH 3.5). Eluant was collected and immediately frozen and stored at −70°C until it was analyzed. The frozen samples containing cefotaxime, desacetylcefotaxime, and internal standard were rapidly thawed, and a 30-μl sample was injected into the high-performance liquid chromatography column.

Chromatographic conditions. Chromatographic conditions were modified from the previously published procedure of Fabre and Kok (6). Separation was accomplished by using a C_{18} reverse-phase column (4.1 by 300 mm, 10 μ) preceded by a C{sub 8} guard column (Alltech Associates, Inc., Deerfield, Ill.). The mobile phase consisted of 90:10 (vol/vol), 0.1 M sodium acetate (pH 4.1) and 0.01 M sodium bromide. The high-performance liquid chromatography analysis was conducted with a Perkin-Elmer (Norwalk, Conn.) model 410 LC pump equipped with a syringe-loading 100-μl sample injector (Rheodyne, model 7125), and elution was at a flow rate of 1.8 ml/min. The effluent was monitored with a variable-wave-length UV detector at 254 nm and a high-performance integrator (LC-90 and LC-100; Perkin-Elmer). The assay sensitivity for cefotaxime and desacetylcefotaxime was 2.5 mg/ml. The interday coefficients of variation were 3.34% at 10 μg/ml and 1.96% at 70 μg/ml.

Pharmacokinetic analysis. Initial polyexponential parameter estimates were obtained by using the ADAPT PC computer software program (3), because it did not require precise initial estimates. Final parameter estimates for cefotaxime were determined by using PCNONLIN (Statistical Consultants, Inc.). In both cases, a unity weighting scheme was used. All model-dependent pharmacokinetic parameters were estimated by using an appropriate adjustment for the infusion period. Model selection criteria were based on the Akaike Information Criterion (21). To determine the elimination rate constant for the metabolite desacetylcefotaxime, a regression of the ratio of the serum desacetylcefotaxime concentration to the area under the concentration-time curve (AUC) of cefotaxime versus the ratio of the AUC of desacetylcefotaxime to the AUC of cefotaxime as described by Houston (11) was used, as follows:

\[
\frac{C(DTX)}{t} = \frac{CL(CTX)}{V(DTX)} - \frac{k_e(DTX)}{\int C(DTX)dt}
\]

where \(t\) is time, \(C\) is the concentration of cefotaxime (CTX) or desacetylcefotaxime (DTX), \(CL\) is clearance, \(V\) is the volume of distribution, and \(k_e\) is the elimination rate constant of desacetylcefotaxime.

Statistical analysis. The results of the data analyses are presented in Table 1 and are shown as mean values ± standard deviations, unless otherwise noted. The Mann-Whitney nonparametric test was used where appropriate. All statistical analyses were done by the methods described by Zar (22). Linear and stepwise regression analyses were performed between selected pharmacokinetic parameters and individual clinical laboratory results to investigate the relationship between hepatic impairment and its influence on drug disposition. A level of \(P < 0.05\) was considered to be statistically significant.

RESULTS

Cefotaxime pharmacokinetics. The serum cefotaxime concentration-time profiles for groups I to V are shown in Fig. 1. The serum cefotaxime concentration-time curves following intravenous infusion were adequately described by using a two-compartment open model based on the Akaike Information Criterion and a sum of squares generally 10 times or greater than when the data were fitted by using a single-compartment open model. The pharmacokinetic parameters derived from these data are given in Table 1. The mean half-life at the elimination phase \(t_{1/2}\) ranged from 2.06 to 4.49 h for the control group (group V) to 2.42 h for group IV. The individual differences in cefotaxime \(t_{1/2}\) for group I, II, III, and IV patients compared with those in the control group (group V) were all statistically significant \((P < 0.05)\) by the Mann-Whitney test.

Cefotaxime AUCs for groups I to V were 176, 192, 241, 217, and 103 μg·h/ml, respectively. The differences in AUC for group II and III patients compared with that for group V patients were statistically significant \((P < 0.05)\); however, the difference in the AUC for group IV patients compared with that for controls was not significant \((P = 0.06)\). The total body clearance, calculated by using a noncompartmen-
tal method, ranged from 2.06 to 4.49 ml/min/kg, with the control group having the highest clearance and group III patients with CPLD and jaundice having the lowest clearance. The steady-state volumes of distribution calculated by using a noncompartmen-
tal method ranged from 0.29 liter/kg for group V (normal) subjects to 0.41 liter/kg in group IV patients. However, the differences in the apparent volumes of distribution in all test groups compared with that in the control group were not statistically significant.

The mean ascitic fluid cefotaxime concentration was 9.90 ± 3.6 μg/ml at 6 h and 1.25 ± 1.6 μg/ml at 24 h for group II patients and 12.95 ± 5.0 μg/ml at 6 h and 1.67 ± 2.6 μg/ml at 24 h for group IV patients.

The clinical laboratory characteristics of the study popula-
tion are given in Table 2. Linear regression analysis be-
tween selected pharmacokinetic parameters and clinical labora-
tory data showed that there was a statistically significant correlation between cefotaxime clearance and the albumin level in serum and an inverse relationship with
alkaline phosphatase. However, correlation of clearance with prothrombin time was not significant ($P = 0.09$). The cefotaxime AUC was inversely related to the albumin concentration in serum. There was a direct relationship between the $t_{1/2}$ of cefotaxime and prothrombin time, but there was an inverse relationship to albumin concentrations in serum.

**Desacetylcefotaxime pharmacokinetics.** Serum desacetylcefotaxime concentration-time profiles for the five groups are shown in Fig. 2. The apparent $t_{1/2}$ for desacetylcefotaxime calculated by using a least-squares regression of the terminal part of the concentration-time curve for groups I to IV were 9.6, 11.4, 7.1, and 13.4 h, respectively; and the $t_{1/2}$ was 2.5 h for the control group. By using a ratio plot, the mean true desacetylcefotaxime $t_{1/2}$ for groups I to V were 1.18, 1.79, 1.48, 1.66, and 1.94 h, respectively, because desacetylcefotaxime demonstrates formation rate-limited kinetics (1, 12). The maximum serum desacetylcefotaxime concentration for each of the five groups ranged from a low of 3 μg/ml in group II to a high of 12.3 μg/ml in group III. The mean desacetylcefotaxime AUCs for groups I to V were 135, 114, 95, and 114 μg · h/ml, respectively.

Desacetylcefotaxime was found to be unstable in solution, because stock solutions stored at 4°C consistently gave standard curves with large inter-run coefficients of variation. Even in samples stored at −20°C, this problem continued to occur. Serum samples containing 5 to 100 μg of desacetylcefotaxime per ml showed 12 to 31% degradation over an 8-h period when they were stored at room temperature. However, desacetylcefotaxime was found to be stable in serum samples stored at −70°C.

**DISCUSSION**

The $t_{1/2}$ (0.78 h) of cefotaxime for the control group (group V) in this study is in agreement with a previously reported value (0.79 h) (14) but differs from others (4, 5, 7, 12), probably because of variation in the lengths of the infusion periods. In patients with CPLD, $t_{1/2}$s were significantly different compared with those in normal control subjects. For example, group IV subjects (with jaundice and ascites) were found to have a significantly longer $t_{1/2}$ in serum (2.42 h) compared with those of the control group. This is in close agreement with that previously reported by Höfken et al. (10) in nine patients with advanced liver disease ($t_{1/2} = 2.3$ h). When patients with limited renal impairment were excluded from the analysis, the differences in the $t_{1/2}$s of group I to IV subjects compared with those of group V subjects were still statistically significant. However, the results of this study differ from the results reported by Graninger et al. (8), who found that the $t_{1/2}$ and AUC of cefotaxime do not differ in patients with cirrhosis compared with the values reported in normal subjects.

The plasma AUC for the control group (AUC = 103 μg · h/ml) was smaller than that reported previously (AUC = 120.7 and 134.1 μg · h/ml) in references 4 and 12, respectively, for identical doses. The lower AUCs for group II and

**TABLE 1. Cefotaxime pharmacokinetic parameters of group I to IV patients compared with those of controls (group V)***

<table>
<thead>
<tr>
<th>Group</th>
<th>$t_{1/2}$ (h)</th>
<th>$t_{1/2}$ (h)</th>
<th>CL (ml/min/kg)</th>
<th>AUC (μg · h/ml)</th>
<th>V (liter/kg)</th>
<th>$C_{max}$ (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.21 ± 0.11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.49 ± 0.41&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.10 ± 0.95</td>
<td>176 ± 74</td>
<td>0.40 ± 0.18</td>
<td>111 ± 38</td>
</tr>
<tr>
<td>II</td>
<td>0.17 ± 0.05&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.69 ± 0.42&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.66 ± 0.64&lt;sup&gt;c&lt;/sup&gt;</td>
<td>192 ± 54&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.39 ± 0.13</td>
<td>128 ± 37</td>
</tr>
<tr>
<td>III</td>
<td>0.17 ± 0.10</td>
<td>1.84 ± 0.37&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.06 ± 0.84&lt;sup&gt;b&lt;/sup&gt;</td>
<td>241 ± 91&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.32 ± 0.11</td>
<td>140 ± 55</td>
</tr>
<tr>
<td>IV</td>
<td>0.27 ± 0.22</td>
<td>2.42 ± 1.87&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.37 ± 0.76&lt;sup&gt;b&lt;/sup&gt;</td>
<td>217 ± 92&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.41 ± 0.13</td>
<td>97 ± 32&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>V</td>
<td>0.09 ± 0.03</td>
<td>0.78 ± 0.19</td>
<td>4.49 ± 1.35</td>
<td>103 ± 21</td>
<td>0.29 ± 0.05</td>
<td>113 ± 10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are means ± standard deviations. $t_{1/2}$, half-life at the distribution phase; $t_{1/2E}$, half-life at the elimination phase; CL, clearance; AUC, area under the concentration-time curve; V, volume of distribution; $C_{max}$, maximum concentration of cefotaxime in serum.

<sup>b</sup> Statistically significant, $P < 0.05$.

<sup>c</sup> $P = 0.06$.**
TABLE 2. Clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>CL\textsubscript{CR} (mL/min)</th>
<th>AST (IU/liter)</th>
<th>ALT (IU/liter)</th>
<th>AlkPhos (IU/liter)</th>
<th>Albumin (g/dl)</th>
<th>Pro-time (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>47 ± 13</td>
<td>71 ± 7</td>
<td>128 ± 41</td>
<td>84 ± 33</td>
<td>42 ± 27</td>
<td>178 ± 70</td>
<td>2.85 ± 0.3</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>41 ± 6</td>
<td>70 ± 5</td>
<td>118 ± 23</td>
<td>85 ± 65</td>
<td>45 ± 35</td>
<td>162 ± 66</td>
<td>2.32 ± 0.6</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>47 ± 13</td>
<td>80 ± 18</td>
<td>125 ± 62</td>
<td>245 ± 281</td>
<td>290 ± 445</td>
<td>252 ± 101</td>
<td>2.98 ± 0.6</td>
<td>32 ± 7</td>
</tr>
<tr>
<td>IV</td>
<td>7</td>
<td>42 ± 9</td>
<td>78 ± 18</td>
<td>107 ± 34</td>
<td>113 ± 67</td>
<td>55 ± 38</td>
<td>200 ± 70</td>
<td>2.33 ± 0.4</td>
<td>41 ± 10</td>
</tr>
<tr>
<td>V</td>
<td>4</td>
<td>33 ± 2</td>
<td>78 ± 13</td>
<td>122 ± 15</td>
<td>63 ± 71</td>
<td>14 ± 3</td>
<td>52 ± 31</td>
<td>4.48 ± 0.4</td>
<td>23 ± 1</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations. CL\textsubscript{CR}, creatinine clearance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AlkPhos, alkaline phosphatase; Pro-time, prothrombin time.

IV patients compared with those for group III patients may have been due to the diffusion of cefotaxime out of the plasma compartment into the ascitic fluid. The greater AUCs in group IV patients compared with those in group II patients (both having ascites) may have been because group IV patients had both ascites and jaundice and a decreased capacity to metabolize cefotaxime. The cefotaxime concentration in ascitic fluid further supports this hypothesis.

Group II patients had a mean ascitic fluid concentration of 9.90 μg/ml at 6 h after infusion; in contrast, group IV patients had a mean ascitic fluid concentration of 12.95 μg/ml at 6 h. In addition, in each patient in groups II and IV, the cefotaxime concentrations in ascitic fluid at 6 and 24 h were consistently higher than their respective levels in plasma taken at the same time. This indicated that cefotaxime freely diffuses into and accumulates in ascitic fluid to an appreciable degree. This finding was also reported by Hary et al. (9), who studied the kinetics of cefotaxime in the peritoneal compartment and concluded that cefotaxime rapidly enters the ascites, with inflow from the intravascular space being more rapid than outflow from the compartment.

The results of this study suggest that the $t_{1/2}$, clearance, and AUC differ in patients with different forms of CPLD. Linear regression analysis demonstrated that changes in $t_{1/2B}$, AUC, and clearance are related to changes in albumin levels in serum, which, generally, is the most accurate predictor of the synthetic capacity of the liver. Desacetylcefotaxime displayed pharmacokinetic behavior similar to that of the parent drug. The apparent $t_{1/2}$ of the metabolite is primarily a function of the disposition of the metabolite into a peripheral compartment and its formation from the parent compound in the liver. The true $t_{1/2}$ of desacetylcefotaxime is shorter than its apparent $t_{1/2}$, since it exhibits formation rate-limited kinetics. Both the apparent $t_{1/2}$ and the true $t_{1/2}$ of desacetylcefotaxime in normal patients ($t_{1/2} = 1.94$ h; apparent $t_{1/2} = 2.5$ h) were longer than those reported previously: $t_{1/2} = 0.83$ h (12) and apparent $t_{1/2} = 0.70$ to 2.44 h (12, 14). These differences could have been due to degradation of desacetylcefotaxime prior to analysis. Although there is decreased metabolic conversion of cefotaxime to desacetylcefotaxime in subjects with hepatic impairment, the apparent $t_{1/2}$ of the metabolite was significantly longer compared with that in normal subjects. This may be due to the fact that desacetylcefotaxime undergoes further metabolism in the normal liver to form secondary metabolites (2, 13, 17).

Serum cefotaxime concentrations at 12 h after infusion in group I to IV patients ranged from 1.33 to 2.57 μg/ml. Piédrola et al. (16) reported that the MIC of cefotaxime against most gram-negative clinical isolates provides inhibition at concentrations of <1.0 μg/ml. Furthermore, a multicenter study (1) found that over 91% of 6,000 clinical isolates of the family Enterobacteriaceae were inhibited by concentrations of cefotaxime of ≤0.5 μg/ml. Moreover, desacetylcefotaxime has antibacterial activity similar to those of expanded-spectrum cephalosporins (1) and is synergistic with cefotaxime for members of the family Enterobacteriaceae susceptible to cefotaxime. These results suggest

FIG. 2. Serum desacetylcefotaxime concentration-time profiles for group I to V patients following a 2-g intravenous infusion of cefotaxime. See legend to Fig. 1 for definitions of symbols.
that impaired production of desacetylcefotaxime may not result in in vivo bactericidal activity below levels that should be effective. The reduced clearance of cefotaxime may have compensated for the altered generation of desacetylcefotaxime.

The results of this study demonstrate that the changes in cefotaxime pharmacokinetic parameters correlate well with the clinical descriptors of hepatic disease. Cefotaxime shows an increase in the AUC and a decrease in clearance in patients with CPLD. Any modest accumulation of cefotaxime in these patients is unlikely to produce toxicity because of its high therapeutic index (1) and will result in the maintenance of therapeutic serum and ascitic fluid bactericidal titers for prolonged periods of time, despite a decreased rate of production of desacetylcefotaxime. Hence, modification of the cefotaxime dose or dosing frequency may not be necessary for most patients with CPLD if the drug is given in usual doses recommended for patients with spontaneous bacterial peritonitis. However, patients with hepatorenal syndrome may require significant dosing modification.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance of Alice Lo and John Tse in assay development and sample analysis. This study was supported in part by a grant from Hoechst-Roussel Pharmaceuticals, Inc.

REFERENCES