Pharmacokinetics of Cefoperazone in the Parturient

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Limited pharmacokinetic data for cefoperazone are available from the parturient. Because cefoperazone has a dual excretory pattern, primarily via the biliary system and secondarily via the kidney, pregnancy-induced physiologic alterations can influence its deposition and clearance. Twelve term parturients receiving cefoperazone prophylaxis after cesarean section were selected for study. After 2 g of cefoperazone was administered for 1 h intravenously, serial blood samples were assayed by high-pressure liquid chromatography. Plasma protein binding of cefoperazone was studied in vitro. The mean peak cefoperazone concentration ± standard deviation was 169.9 ± 60.4 μg/ml. The mean half-life was 152 min. Total serum clearance was 80.8 ± 30.8 ml/min. The steady-state volume of distribution was 14.2 ml/kg. All subjects had detectable trough levels at the end of the dosage interval, with a mean value of 65.5 ± 5.2 μg/ml. Protein binding of cefoperazone for parturients was 74.3 ± 10.9%, compared with 87.7 ± 3.2% in nonpregnant controls (P < 0.05). These data suggest that cefoperazone deposition can be greatly influenced by pregnancy. However, unlike several other new antimicrobial agents whose excretions are normally renal, the cefoperazone half-life and thus trough concentration for the parturient more closely resemble that for the nonpregnant subject.

Cefoperazone has been shown to be efficacious in a variety of clinical settings by virtue of its broad range of antibacterial activity. In particular, because the obstetric patient who develops post-caesarean-section sepsis is most often infected by a polymicrobial insult, broad-spectrum antimicrobial agents have justified the single-dose approach of the clinician to therapy (4, 12). However, recognition of physiologic alterations which normally occur in the parturient is important, because these changes may directly influence the pharmacokinetic behavior of a given drug and therefore its clinical utility (10). In this regard, cefoperazone has been shown to exhibit an excretion pattern primarily via the biliary system and secondarily through the kidneys (3). Because these excretory pathways may be altered during pregnancy, a study was undertaken to evaluate the pharmacokinetics of cefoperazone in this select study population.

MATERIALS AND METHODS

Subjects. Twelve term parturients who underwent cesarean section by the obstetric service staff at Hermann Hospital, the major teaching institution for the University of Texas Medical School at Houston, were enrolled in this prospective research study. The protocol was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston and the University of Houston-University Park. All patients received cefoperazone for prophylaxis at the time of surgery and again 12 h postoperatively. Each subject was studied at the time of the latter drug administration period. After informed consent was obtained, 2 g of cefoperazone were administered over 60 min with an intravenous infusion pump. Blood samples were collected via a heparin lock before the infusion was started; additional blood samples were obtained at 0.5, 1, 1.5, 2, 3, 4, 9, and 12 h after initiation of the infusion. Samples were centrifuged, and sera were frozen at −20°C until analyzed. Total urine samples were collected over the dosage interval, and an aliquot was stored at −20°C until analyzed.

Protein-binding experiments. Plasma samples were obtained from 9 healthy, reproductive-age (21 to 34 years) nonpregnant women and from 11 additional parturients in the immediate postpartum period after uncomplicated cesarean section. All samples were placed in heparinized tubes, centrifuged, and stored at −20°C until used in the experiment.

Cefoperazone was added to each plasma sample to yield a final antibiotic concentration of 100 μg/ml. The samples were placed in an ultrafiltration system (Centrifree, Amicon Corp.), incubated at 37°C for 20 min, and then centrifuged at 2,000 × g for 2 min. The entire sequence was carried out in a thermostated room at 37°C.

Assay. Total and free concentrations of cefoperazone in plasma and serum samples were determined by a modification of the high-pressure liquid chromatographic method of Kimmerich et al. (6). The method involves the precipitation of plasma proteins with ice-cold methanol and the separation and quantitation of cefoperazone on a reversed-phase ODS 5-μ column at a flow rate of 2 ml/min, with detection at 254 nm. The mobile phase consisted of 0.01 M sodium acetate and 18% acetonitrile at pH 4.0. The intra- and inter-day coefficient of variation was less than 5%. Urine concentrations of cefoperazone were also analyzed by the above methodology. Total protein was measured by the method of Lowry et al. (7). Serum albumin was determined by a colorimetric method involving the binding of brom cresol green to the protein molecule (Sigma Diagnostic).

Data analysis. Concentration-time data for sera were analyzed by model-independent methods. The half-life (t½) was determined from the slope (β) of the terminal log-linear portion of the cefoperazone concentration in sera versus the
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FIG. 1. Time-concentration curve for cefoperazone (mean ± SD) after administration of 2 g intravenously over 1 h to postpartum subjects.

time curve, as shown by \( t_{1/2} = 0.693/\beta \). Clearance (CL) was calculated as follows: \( \text{CL} = \text{dose/AUC} \), for which AUC is the area under cefoperazone concentration-time curve for serum specimens during the dosage interval.

The steady-state volume of distribution (\( V_{ss} \)) was calculated from the following relationship: \( V_{ss} = \text{dose} \times (\text{AUMC}/(\text{AUC})^2 - \text{dose}/(T)/2(\text{AUC}) \), for which AUMC is the total area under the first moment of the concentration-time curve and \( T \) is the duration of the infusion. An assumption was made in all calculations that cefoperazone concentrations were at steady state. Renal clearance (\( \text{CLR}_R \)) of cefoperazone was calculated as \( \text{CLR}_R = \text{amount of urine/AUC} \). The percentage of cefoperazone bound to plasma proteins was calculated by \% Bound = \( (C_f - C_p)/C_f \times 100 \), for which \( C_f \) represents the total cefoperazone concentration in plasma and \( C_p \) is the free-drug concentration. Values between groups were compared by unpaired \( t \)-test analysis.

RESULTS

The mean age ± standard deviation (SD) of the subjects studied was 27.3 ± 5.0 years. All patients had completed 37 weeks of uncomplicated pregnancy. Indications for abdominal delivery included cephalopelvic disproportion (\( n = 7 \)), malpresentation (\( n = 2 \)), and fetal distress (\( n = 3 \)). None of these subjects had histories of renal or biliary compromise before or during the current pregnancy.

Serum samples were analyzed for cefoperazone content by high-pressure liquid chromatography. A plot of the mean concentrations (± SDs) of cefoperazone in sera at each time period during the dosage interval is shown in Fig. 1. The mean peak concentration ± SD of cefoperazone in sera after infusion of the 2-g dose was 169.9 ± 60.4 \( \mu \text{g/ml} \). The mean trough level at the end of the dosage interval was 6.5 ± 5.2 \( \mu \text{g/ml} \). The mean cefoperazone concentration in sera at the start of the dosage interval (\( t = 0 \)) was 7.4 ± 6.3 \( \mu \text{g/ml} \). This was not significantly different (\( P > 0.05 \)) from that of the trough level. This and the fact that the cefoperazone dosage was administered at approximately five times the \( t_{1/2} \) lead us to assume that the drug was at steady state.

Mean total clearance ± SD of cefoperazone in the serum specimens of the study group was 80.8 ± 30.8 ml/min and was 1.1 ± 0.4 ml/min per kg when corrected for body weight. The volume distribution was 14.2 ± 6.0 liters or 0.18 ± 0.04 liters/kg. Analysis of the terminal portion of the cefoperazone concentration-time curve for sera yielded a mean \( t_{1/2} \) of 152 min. The pharmacokinetic parameters calculated from this study are listed in Table 1, along with patient characteristics.

The percentages of cefoperazone which bound to plasma proteins in women who were not pregnant or who were 1-day postpartum are listed in Table 2. Also included in this table are the total protein concentrations for each group, as well as the plasma albumin concentrations. A significant (\( P < 0.05 \)) decrease (–15.3%) in cefoperazone binding occurred during the immediate postpartum period compared to binding in the nonpregnant state. Total protein concentration also was significantly (\( P < 0.05 \)) decreased immediately postpartum when compared with that of nonpregnant controls (Table 2).

DISCUSSION

Cefoperazone is an interesting drug to examine with respect to the parturient because its deposition characteristics differ from that of other cephalosporins. Cefoperazone is eliminated by both renal and nonrenal mechanisms; it has been reported to be excreted mainly in bile, with renal excretion accounting for only 14 to 36% of a dose (3, 6). Although some alteration in biliary function occurs with pregnancy, this change is small compared with known increases which occur in the glomerular filtration rate of the gravida (8).

The \( t_{1/2} \) of cefoperazone (152 min) determined from the present study is similar to values (100 to 160 min) reported from other studies of cefoperazone pharmacokinetics in

<table>
<thead>
<tr>
<th>Age (yr) of patient(^a)</th>
<th>W(_t) (kg)(^b)</th>
<th>( t_{1/2} ) (min)</th>
<th>CL(_{ss}) (ml/min per kg)</th>
<th>CL(_p) (ml/min per kg)</th>
<th>V(_ss) (liter/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>62.7</td>
<td>135</td>
<td>1.31</td>
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<tr>
<td>24</td>
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<td>0.85</td>
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<tr>
<td>34</td>
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<td>1.15</td>
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<td>0.27</td>
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<tr>
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<td>0.16</td>
</tr>
<tr>
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<tr>
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<td>177</td>
<td>0.70</td>
<td>0.38</td>
<td>0.16</td>
</tr>
<tr>
<td>30</td>
<td>76.8</td>
<td>231</td>
<td>0.54</td>
<td>0.46</td>
<td>0.16</td>
</tr>
</tbody>
</table>

\( ^a \) Mean age (±SD) was 27.3 (±5.0) years.

\( ^b \) Mean weight (±SD) was 77.0 (±20.6) kg.

\( ^c \) Mean parameters (±SDs) were 152 min (harmonic mean) for \( t_{1/2} \), 1.1 (0.4) ml/min per kg for CL\(_{ss} \), 0.37 (0.12) ml/min per kg for CL\(_p\), and 0.18 (0.04) liters/kg for V\(_ss \). CL\(_T\), Total clearance; CL\(_R\), renal clearance; V\(_ss\), volume of distribution at steady state.

Table 1. Pharmacokinetic parameters of cefoperazone in 12 postpartum subjects.

\( ^a \) Mean age (±SD) was 27.3 (±5.0) years.

\( ^b \) Mean weight (±SD) was 77.0 (±20.6) kg.

\( ^c \) Mean parameters (±SDs) were 152 min (harmonic mean) for \( t_{1/2} \), 1.1 (0.4) ml/min per kg for CL\(_{ss} \), 0.37 (0.12) ml/min per kg for CL\(_p\), and 0.18 (0.04) liters/kg for V\(_ss \). CL\(_T\), Total clearance; CL\(_R\), renal clearance; V\(_ss\), volume of distribution at steady state.
TABLE 2. Cefoperazone protein binding and total protein concentrations in nonpregnant and postpartum subjects

<table>
<thead>
<tr>
<th>Patient status</th>
<th>No. of patients</th>
<th>Protein % Bound</th>
<th>Mean total concn ± SD (g/100 ml)</th>
<th>Protein %Change</th>
<th>Mean total albumin concn ± SD (g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant</td>
<td>9</td>
<td>87.7 ± 3.2</td>
<td>7.52 ± 0.99</td>
<td></td>
<td>3.33–4.54b</td>
</tr>
<tr>
<td>Postpartum</td>
<td>11</td>
<td>74.3 ± 10.9a</td>
<td>-15.3</td>
<td>4.34 ± 1.65c</td>
<td>-42.3</td>
</tr>
</tbody>
</table>

* Normal range.  
*b P < 0.05 compared with value for nonpregnant subjects t test.

humans (3, 6). In our study population, the mean total clearance ± SD of cefoperazone was 1.1 ± 0.4 ml/min per kg, in good agreement with the clearance of 0.98 ml/min per kg, reported by Kimmerich et al. (6). This consistency with values for nonpregnant women is in distinction from pharmacokinetic studies with cefotixin and cefotaxime, in which both agents were determined to have high clearances in the sera of postpartum subjects compared with those of nonpregnant controls (1, 2). The mean renal clearance value ± SD calculated from the data obtained in the present investigation was 0.37 ± 0.12 ml/min per kg. This value is slightly higher than the renal clearance for cefoperazone of 0.25 ml/min per kg reported by others (5). In our study population, renal clearance accounted for 39% of the clearance of cefoperazone in serum specimens. This represents a greater fraction of the total clearance of the drug being cleared by the kidneys than has been reported in previous studies (11). The increase in renal clearance of cefoperazone in the postpartum patient is consistent with known physiologic alterations in renal function during pregnancy, as indicated earlier (8).

The mean state-state volume of distribution ± SD of cefoperazone in our postpartum patient population was 14.2 ± 6.0 liters or 0.18 ± 0.04 liters/kg. This value is slightly higher than the Vss reported by Standiford et al. (11) of 0.14 ± 0.02 liters/kg and may suggest altered distribution of cefoperazone in the postpartum subject. This effect may be due to an increase in extracellular water or to altered protein binding of cefoperazone. While it is recognized that extracellular water volume increases during pregnancy and appears to be responsible for alterations observed in drug distribution (1, 2, 10), the influence of a decrease in protein binding could play a role in the observation of greater distribution of cefoperazone in the postpartum patient. The altered binding of drugs during pregnancy has been reported for diazepam and salicylate (13). In both cases, an increase in the drug-free fraction was found in sera from pregnant women. This was found to be related to a decreased albumin concentration in the sera.

It is worthwhile to determine MICs of cefoperazone for various organisms in this particular setting. Specifically, cefoperazone has been approved for use in enterococcal infections, a not uncommon endometrial organism identified in tests of infected postpartum patients. However, at a reported MIC for 90% of strains at 32 to 64 μg/ml (9, 12), this agent quickly falls below these minimum values when administered as a 2-g bolus dose (see Fig. 1). Although many infections may be adequately controlled with concentrations in sera not consistently above the MIC for the infecting organism(s), these data suggest that cefoperazone not be used as a first-line drug for enterococcus-associated sepsis.

Although it is difficult to directly compare different studies, due to differences in methodology and study design, our data suggest that drug deposition can be greatly influenced by pregnancy and that these findings may be of importance for determining correct dosages and other therapy for the postpartum patient. Our results demonstrate larger volumes of distribution, lower peak concentrations, and lower plasma protein binding than previously reported (3, 6). However, unlike other new antimicrobial agents whose excretions are mainly renal, the cefoperazone t1/2 and subsequent trough levels for the parturient more closely resemble those of the nonpregnant subject.

LITERATURE CITED