Pharmacokinetics of Intravenous Piperacillin Administration in Patients Undergoing On-Line Hemodiafiltration

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The pharmacokinetic characteristics of piperacillin sodium were studied in five volunteers undergoing on-line hemodiafiltration (HDF). The subjects were given 2 g of piperacillin sodium intravenously over 1 min and placed on on-line HDF for 4 h starting at 60 min after the piperacillin infusion. Noncompartmental models were employed for estimation of the pharmacokinetic parameters, and intradialytic piperacillin clearance was calculated by the recovery method. The mean volume of distribution and the elimination half-life were 0.27 ± 0.13 liter/kg (mean ± standard deviation) and 1.1 ± 0.6 h, respectively. The total body clearance of piperacillin was 0.19 ± 0.08 liter/h/kg. Piperacillin clearance through on-line HDF was 0.11 ± 0.06 liter/h/kg. The mean serum piperacillin concentration was 4.0 ± 1.9 μg/ml at the end of the 4-h on-line HDF session. The concentration of infused piperacillin recovered in the dialysate was 527 ± 236 mg (26.3% ± 11.8%). We suggest the replacement of 500 mg of piperacillin after each on-line HDF session.

Piperacillin, a piperazine derivative of ampicillin, has in vitro activity against clinically relevant gram-positive and gram-negative bacteria (7, 18). It is known to inhibit most of the clinically important members of the family Enterobacteriaceae, such as Escherichia coli, Enterobacter cloacae, and Proteus mirabilis, and approximately half of the isolates of Klebsiella pneumoniae. In addition, it is four- to eightfold more active than carbenicillin in inhibiting Pseudomonas aeruginosa (7, 15). This wide spectrum and potent antipseudomonal activity make piperacillin useful. Clinically, it is prescribed for the treatment of neutropenic fever in combination with tobramycin. When it is formulated in combination with tazobactam, a beta-lactamase inhibitor (Tazocin), piperacillin is widely used for the treatment of hospital-acquired and other serious infections.

Current guidelines for piperacillin dosing are based on the results of studies conducted in the 1970s with low-flux hemodialysis. Considerable changes in hemodialyzer membrane compositions and dialytic techniques have occurred since then. Recent years have seen the wide acceptance of high-flux hemodialysis and on-line hemodiafiltration (HDF). On-line HDF is an extracorporeal technique for solute removal in patients with renal failure and takes advantage of the enhancement of convective treatment by the large amount of ultrapure nonpyrogen dialysis fluid being used for substitution of the ultrafiltered volume. However, research on piperacillin removal by the newer dialysis technique has not kept pace. Piperacillin (molecular mass, 516.5 Da) is large enough that its dialytic clearance would likely be influenced by the dialysis technique. For these reasons, we studied the pharmacokinetics of piperacillin administered intravenously to five volunteers undergoing on-line HDF. The purpose of this study is twofold: (i) to characterize the pharmaco-kinetics and dialytic clearance of piperacillin by on-line HDF in otherwise healthy subjects with end-stage renal disease and (ii) to develop strategies for piperacillin dosing in those subjects placed on on-line HDF.

MATERIALS AND METHODS

Subjects. Five patients (four men, one woman) who were 50 to 70 years of age, anuric (defined as urine output of less than 100 ml/day), and undergoing chronic, intermittent hemodialysis were enrolled in the study. No patient had a history of allergic reaction to any penicillin or hepatobiliary disease, and no patient had received an antimicrobial agent within 30 days before inclusion in the study. The study protocol was approved by the Institutional Review Board of the Seoul National University Hospital, and written informed consent was obtained from each subject before entry into the study.

Procedures. All study procedures were conducted in the outpatient dialysis unit at Seoul National University Hospital. A 2.0-g intravenous dose of piperacillin sodium (Yuhan, Seoul, South Korea) in 10 ml of 0.9% saline was given over 1 min at 1 h before the dialysis period. Venous blood specimens were obtained at 1, 5, 10, 15, 20, 30, and 45 min after the piperacillin administration. Dialysis was started 60 min after the administration of piperacillin to allow the drug to evenly distribute in the body before the start of dialysis. All patients were dialedyzed for 4 h with on-line HDF (AK 200 Ultra S; Gambro, Lund, Sweden). Blood flow was maintained at a constant rate of 300 ml/min. The dialysate flow rate was held constant at 600 ml/min. Replacement fluid was supplied by the postdilution method. The replacement fluid volume was determined by the equation 21.6 liters minus the ultrafiltration volume. Arterial blood specimens were obtained at 60 min (the start of dialysis); 70, 80, 90, 105, 120, 180, and 240 min; and 300 min (the end of dialysis). Dialysate was collected hourly during the dialysis. Blood was collected in evacuated glass tubes and was allowed to clot at room temperature, and the serum was separated by centrifugation. All serum and dialysate samples were stored frozen at −70°C until analysis.

Determination of piperacillin concentration. The concentrations of piperacillin in serum and dialysate were determined by high-performance liquid chromatography with UV detection by a previously validated method (2).
The pharmacokinetics of intravenously administered piperacillin have been described in healthy patients (3, 5, 11); patients with decreased renal function (8, 19); patients undergoing hemodialysis (6, 8); and patients experiencing continuous venovenous hemofiltration (17), continuous venovenous hemodialysis (12), and continuous venovenous hemodiafiltration (16). However, they have not been investigated in patients undergoing on-line HDF, which has been adopted in many dialysis centers around the globe. To the best of our knowledge, this is the first study that evaluated the pharmacokinetic properties of an antibiotic in patients undergoing on-line HDF.

In our study, the mean intradialytic clearance during on-line HDF was 0.11 liter/h/kg or 7.44 liters/h per 1.73 m². This was higher than that achieved during conventional hemodialysis reported elsewhere, which was 0.09 liter/h/kg (6) or 0.484 liter/h per 1.73 m² (8). This may be in accordance with our assumption that the addition of convection to the diffusion method increases the clearance of piperacillin. Hemofiltration often removes large molecules (molecular masses, >500 Da) better than hemodialysis does. However, our study is based on a pharmacokinetic model and a population different from those used in the studies described above (6, 8). In order to verify our assumption, drugs with molecular masses larger than 500 Da, i.e., vancomycin, teicoplanin, etc., need to be investigated for their pharmacokinetic profiles during on-line HDF in the future.

There is a noteworthy point about the methods used in the various studies: other studies administered piperacillin immediately prior to the dialysis session. However, in the present study, dialysis was started 1 h after drug administration to allow an even distribution of piperacillin in the body. The clearance achieved in this study might have been increased further, had the 1 h for the drug distribution been omitted, as in the other studies. However, in the actual clinical setting, antibiotics are not usually administered right before a dialysis session. Therefore, the pharmacokinetics of piperacillin during on-line HDF were studied in this study.

**RESULTS**

The characteristics of the study participants are listed in Table 1. The mean age was 60.4 years, and there were four male patients and one female patient. No subjects exhibited adverse effects from the study drug. The concentration of piperacillin in the dialysate was measured for all subjects except patient 5. For one patient (patient 5), determination of the dialysate concentration was not conducted because some of the dialysate samples were missing. Figure 1 shows the change in the serum piperacillin concentration over time after intravenous injection. The values of the pharmacokinetic parameters for piperacillin are shown in Table 2. The mean volume of distribution was 0.27 ± 0.13 liter per kg of body weight (mean ± standard deviation). The mean total clearance was 0.19 ± 0.08 liter/h/kg, and the serum half-life was 1.1 ± 0.6 h. The mean intradialytic clearance during on-line HDF was 0.11 ± 0.06 liter/h/kg. At the end of 4 h of on-line HDF, the serum piperacillin concentration was 4.0 ± 1.9 µg/ml. During the 4-h on-line HDF, 527 ± 236 mg (26.3% ± 11.8%) of the piperacillin infused was recovered in the dialysate. The simulation for various doses of postdialysis piperacillin replacement included (i) no replacement, (ii) the replacement of 500 mg, and (iii) the replacement of 750 mg in a setting of regular intravenous administration of 2 g piperacillin every 6 h in patients placed on on-line HDF. The proportions of the time that the serum concentration remained above the MIC were 56.9%, 63.0%, and 65.6% during dialysis for no replacement, replacement of 500 mg, and replacement of 750 mg, respectively.

**DISCUSSION**

**TABLE 1. Demographic data for the subjects**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Dry wt (kg)</th>
<th>Ht (cm)</th>
<th>BSA (m²)</th>
<th>Ultrafiltration vol (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>65.0</td>
<td>171</td>
<td>1.76</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>71.3</td>
<td>172</td>
<td>1.83</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>M</td>
<td>78.9</td>
<td>174</td>
<td>1.93</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>56.6</td>
<td>157.6</td>
<td>1.56</td>
<td>1.2</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>F</td>
<td>58.8</td>
<td>157</td>
<td>1.58</td>
<td>3.2</td>
</tr>
</tbody>
</table>

a M, male; F, female.  
b BSA, body surface area.

Quantification was 2.5 µg/ml, and the between-run coefficient of variation was 10.7% at 40 µg/ml.

Pharmacokinetic analysis. The data were analyzed by noncompartmental methods. Serum elimination half-lives, areas under the serum concentration-time curves, and volumes of distribution were determined by computer-aided regression for a noncompartmental model (WinNonlin, Professional Network, version 5.2; Pharsight Corporation). The elimination coefficient was determined after visual identification of the terminal log-linear phase of each individual serum log concentration-time curve.

Intradialytic piperacillin clearance was calculated by using the recovery method and the following relationship: \( CL_{HDF} = \frac{R}{AUC_{HDF}} \), where \( CL_{HDF} \) is the piperacillin clearance through on-line HDF, \( R \) is the amount of piperacillin recovered during the dialysis session, and \( AUC_{HDF} \) is the area under the serum concentration-time curve during on-line HDF.

Time-plasma concentration profiles were simulated, and the times above the MIC (16 µg/ml) were calculated by using the Trial Simulator program (version 2.2; Pharsight Corporation) in order to compare the various regimens for a candidate replacement dose. During model building, a two-compartment model with reference population pharmacokinetic parameter values and model-fitting criteria were used (4, 9, 14). Simulations of 1,000 patients for each regimen were performed by using a computer-based data resampling method.

**FIG. 1. Mean serum piperacillin levels after intravenous administration.** At 0 min, 2 g of piperacillin was given intravenously over 1 min. The subjects were placed on on-line HDF from 60 min to 300 min. Error bars denote standard deviations.
fore, we suggest that enough time between drug administration and the start of dialysis be allowed when a pharmacokinetic study associated with various renal replacement therapies is being designed.

In addition, a review of previous studies showed other notable points that might be useful when the results of different studies are compared or when the results of pharmacokinetic studies are put into practice. First, different piperacillin doses (15 mg/kg versus 60 mg/kg or 1 g versus 4 g) did not result in differences in the values of the pharmacokinetic parameters achieved (1, 19). Second, the pharmacokinetics of piperacillin remained unaffected by tazobactam when they were given together at a ratio of 8:1 (13).

In the present study, dosing of 2 g of piperacillin 1 h before on-line HDF resulted in a serum piperacillin concentration of 4.0 ± 1.9 μg/ml at the end of the 4-h dialysis session. It is way below the breakpoint MIC of 16 μg/ml for pathogens such as the members of the family Enterobacteriaceae and Pseudomonas spp. (10). In our study, it was shown that 527 ± 236 mg (26.3% ± 11.8%) of the piperacillin infused was removed during 4-h on-line HDF. Our simulation shows that the replacement of 500 mg of piperacillin after on-line HDF would result in a proportion of the time that the serum concentration remained above the MIC of 63.0% during on-line HDF. Thus, we suggest the replacement of 500 mg of piperacillin after each on-line HDF session.

Although our study subjects were given piperacillin as a single formula, the combination of piperacillin and the beta-lactamase inhibitor tazobactam is often prescribed for critically ill patients. With their low levels of protein binding (20 to 30%), both drugs are normally excreted through the urine and have similar pharmacokinetic properties. Besides, the pharmacokinetic behavior of piperacillin is the same whether it is given alone or in combination with tazobactam (i.e., they have no pharmacokinetic interaction) (13). Therefore, the replacement of a proportionate dose of tazobactam after each on-line HDF session could be considered for patients treated with piperacillin-tazobactam.

REFERENCES


<table>
<thead>
<tr>
<th>Subject no.</th>
<th>V (liter/kg)</th>
<th>CLtot (liter/h/kg)</th>
<th>Half-life (h)</th>
<th>AUCINF (mg · h/liter)</th>
<th>kelim (1/h)</th>
<th>AUCHEDF (mg · h/liter)</th>
<th>CLHEDF (liter/h/kg)</th>
<th>R (mg)</th>
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<tr>
<td>1</td>
<td>0.24</td>
<td>0.23</td>
<td>0.7</td>
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<td>0.93</td>
<td>60.0</td>
<td>0.13</td>
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<tr>
<td>2</td>
<td>0.10</td>
<td>0.18</td>
<td>0.4</td>
<td>153.7</td>
<td>1.89</td>
<td>64.6</td>
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<td>3</td>
<td>0.20</td>
<td>0.08</td>
<td>1.7</td>
<td>306.2</td>
<td>0.42</td>
<td>95.7</td>
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<tr>
<td>4</td>
<td>0.44</td>
<td>0.18</td>
<td>1.7</td>
<td>201.9</td>
<td>0.40</td>
<td>79.0</td>
<td>0.09</td>
<td>395</td>
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<tr>
<td>5</td>
<td>0.35</td>
<td>0.30</td>
<td>0.8</td>
<td>113.7</td>
<td>0.85</td>
<td>65.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.27 ± 0.13</td>
<td>0.19 ± 0.08</td>
<td>1.1 ± 0.6</td>
<td>182.3 ± 76.5</td>
<td>0.90 ± 0.60</td>
<td>72.9 ± 14.6</td>
<td>0.11 ± 0.06</td>
<td>527 ± 236</td>
</tr>
</tbody>
</table>

* V, volume of distribution; CLtot, total body clearance of piperacillin; AUCINF, area under the concentration-time curve for an infinite time; kelim, elimination rate constant; AUCHEDF, area under the concentration-time curve during on-line HDF; CLHEDF, piperacillin clearance through on-line HDF; R, amount of piperacillin recovered during the on-line HDF session; SD, standard deviation.

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