Pharmacokinetics of Intravenous Piperacillin Administration

in Patients Undergoing On-line Hemodiafiltration

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Abstract

The pharmacokinetic characteristics of piperacillin sodium were studied from five volunteers undergoing on-line hemodiafiltration (HDF). Subjects were given 2 grams of piperacillin sodium intravenously over 1 min and placed on on-line HDF for 4 hours starting at 60 min after piperacillin infusion. Non-compartment models were employed for estimation of pharmacokinetic parameters, and intradialytic piperacillin clearance was calculated using the recovery method. Mean volume of distribution and elimination half life was 0.27±0.13 L/kg (mean ± standard deviation) and 1.1±0.6 hr, respectively. Total body clearance of piperacillin was 0.19±0.08 L/hr/kg. Piperacillin clearance through on-line HDF was 0.11±0.06 L/hr/kg. Mean serum concentration of piperacillin at the end of 4 hour on-line HDF was 4.0±1.9 μg/mL at the end of 4-hour dialysis session. 527±236 mg (26.3±11.8%) of the piperacillin infused was recovered in the dialysate. We suggest replacing 500 mg of piperacillin after each on-line HDF session.

KEYWORDS : piperacillin, on-line hemodiafiltration, pharmacokinetic
Introduction

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 Enterobacteriaceae, such as Escherichia coli, Enterobacter cloacae, Proteus mirabilis and approximately half of the 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 makes piperacillin useful. Clinically, it is prescribed for neutropenic fever in combination with tobramycin. When formulated in combination with tazobactam, a beta-lactamase inhibitor as Tazocin®, piperacillin is widely used for hospital acquired infection or other serious infection.

Current guidelines for piperacillin dosing are based on studies conducted in the 1970s with low flux hemodialysis. Considerable changes in hemodialyzer membrane composition and dialytic technique have occurred since then. Recent years have seen wide acceptance of high flux hemodialysis and on-line hemodiafiltration (HDF). On-line HDF is an extracorporeal technique for solute removal in renal failure, which takes advantage of an enhancement of convective treatment by the large amount of ultrapure nonpyrogen dialysis fluid being used for substitution of the ultrafiltered volume. But, research for piperacillin removal by the newer dialysis technique has not kept pace. Piperacillin (molecular weight, 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: (1) to characterize the pharmacokinetics and dialytic clearance of piperacillin by on-line HDF in otherwise healthy subjects with end-stage renal disease, and (2) to develop strategies for piperacillin dosing in those subjects placed on on-line HDF.

Subjects and Methods

Subjects

Five patients, aged 50 to 70 years (4 men, 1 women), anuric, defined as urine output less than 100mL/day and undergoing chronic, intermittent hemodialysis were enrolled onto the study. No patient had a prior history of allergic reaction to any penicillin or hepatobiliary disease, or had received an antimicrobial agent within 30 days before inclusion in the study. The study protocol was approved by the institutional review board of Seoul National University Hospital and written informed consent was obtained from each subject before entry onto 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, Korea) in 10 ml of 0.9% saline was given over 1 minute, at 1 hour before the dialysis period. Specimens of venous blood 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 for an even distribution of the drug in the body before starting dialysis. All patients were dialyzed 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. Dialysate flow rate was held constant at 600 mL/min. Replacement fluid was supplied using post-dilution method. The replacement fluid volume was determined by an equation ‘21.6 liter minus the ultrafiltration volume’. Specimens of arterial blood were obtained at 60 (start of dialysis), 70, 80, 90, 105, 120, 180, 240, and 300 min (end of dialysis). Dialysate was collected hourly during the dialysis. Blood was collected in evacuated glass tubes and 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
Concentrations of piperacillin in serum and dialysate were determined by high performance liquid chromatography with UV detection, following a previously validated method (2). The limit of quantification was 2.5 µg/mL and the between-run coefficient of variation was 10.7% at 40 µg/mL.

Pharmacokinetic analysis
Data were analyzed using non-compartmental methods. Serum half-lives (T1/2 β), areas under the serum concentration-time curve (AUC), and volume of distribution were determined using computer-aided regression for a non-compartment model (WinNonlin; Professional Network Version 5.2; Pharsight Corporation, CA, USA). The elimination coefficient (k_e) was determined after visual identification of the terminal log-linear phase of each individual serum log concentration-time curve.
Intradialytic piperacillin clearance was calculated using the recovery method and the following relationship: CL_{HDF} = 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 times above MIC (16 µg/mL) were calculated using Trial Simulator (ver 2.2 Pharsight Co, CA, USA), in order to compare 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, using a computer-based data resampling method.
**Results**

The characteristics of the study participants are listed in Table 1. The mean age was 60.4 years old, and there were 4 male and 1 female patients. No subjects exhibited adverse effects from the study drug. Dialysate concentration of piperacillin was measured from all subjects except patient #5. For one patient (# 5), determination of dialysate concentration was not conducted because some of the dialysate samples were missing. Fig 1 shows the change of serum concentration of piperacillin over time after intravenous injection. Pharmacokinetic parameters for piperacillin are shown in Table 2. Mean volume of distribution was 0.27±0.13 L per kg of body weight (mean±SD). Mean total clearance was 0.19±0.8 L/hr/kg with serum half life of 1.1±0.6 hr. The mean intradialytic clearance using on-line HDF was 0.11±0.06 L/hr/kg. At the end of 4 hour on-line HDF, serum concentration of piperacillin was 4.0±1.9 µg/mL. During a 4-hour on-line HDF, 527±236 mg (26.3±11.8%) of the piperacillin infused was recovered in the dialysate. Simulation for various doses of post-dialysis piperacillin replacement included 1) no replacement, 2) 500 mg, and 3) 750 mg replacement in a setting of regular intravenous administration of 2 g piperacillin every 6 hours in patients placed on on-line HDF. The percentage of time that the serum concentration remains above MIC (%T>MIC) were 56.9%, 63.0% and 65.6% during dialysis for no replacement, 500 mg and 750 mg replacement, respectively.

**Discussion**

The pharmacokinetics of intravenously administered piperacillin have been described in normal patients (3, 5, 11), patients with decreased renal function (8, 19), patients undergoing hemodialysis (6, 8) and patients experiencing continuous venovenous hemofiltration (CVVH) (17), -hemodialysis (CVVHD) (12) and –hemodiafiltration (CVVHDF) (16). But it has 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 pharmacokinetic properties of an antibiotic drug in patients undergoing on-line HDF. The mean intradialytic clearance during on-line HDF was 0.11 L/hr/kg or 7.44L/hr per 1.73m² in our study. This was higher than that of conventional hemodialysis reported elsewhere, which was 0.09 L/hr/kg (6) or 0.484 L/hr per 1.73m² (8). This may be in accordance with our assumption that adding convection to the diffusion method increases the clearance of piperacillin. Hemofiltration often removes large molecules (M.W. > 500 Da) better than hemodialysis. However, our study is based on a different pharmacokinetic model and a different population, compared to the above studies(6, 8). In order to verify our assumption, drugs with
molecular weight larger than 500 dalton - vancomycin, teicoplanin, etc - need to be investigated for the pharmacokinetic profiles during on-line HDF in the future.

There is a point of note in methods of study: other studies administered piperacillin immediately prior to the dialysis session. However, in this study, dialysis was started 1 hour after the drug administration to allow for an even distribution of piperacillin in the body. The clearance value in this study might have been increased further, had the 1 hour for the drug distribution been omitted like other studies. However, in the actual clinical setting, antibiotics are not usually administered right before dialysis session. Therefore, we suggest that enough time should be allowed for between drug administration and start of dialysis when designing a pharmacokinetic study associated with various renal replacement therapies.

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

In the present study, dosing of 2 grams of piperacillin, administered 1 hour before on-line HDF, resulted in a serum piperacillin concentration of 4.0±1.9 µg/mL at the end of 4-hour dialysis session. It is way below breakpoint MIC of 16 µg/mL for pathogens such as 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-hour on-line HDF. Our simulation shows 500 mg replacement after on-line HDF would result in %T>MIC of 63.0% during on-line HDF. Thus, we suggest replacing 500 mg of piperacillin after each on-line HDF session.

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


### Table 1. Demographic Data of the subjects

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<th>Sex</th>
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<th>Height (cm)</th>
<th>BSA(^{\text{a}})(m(^2))</th>
<th>Ultrafiltration volume (L)</th>
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\(^{\text{a}}\)BSA : Body surface area
Fig 1. Mean piperacillin serum levels after intravenous administration.
At 0 min, 2 g of piperacillin was given intravenously over 1 min. Subjects were placed on on-line HDF from 60 min until 300 min. Error bar denotes standard deviation.
Table 2. Pharmacokinetic parameters of piperacillin undergoing on-line HDF

| Subject No. | Vd (L/kg) | CL$_{tot}$ (L/hr/kg) | Half-life (hr) | AUC$_{INF}$ (hr·mg/L) | $k_{el}$ (1/hr) | AUC$_{HDF}$ (hr·mg/L) | CL$_{HDF}$ (L/hr/kg) | R (mg) | SD ±
|-------------|-----------|----------------------|----------------|-----------------------|----------------|------------------------|----------------------|--------|------
| 1           | 0.24      | 0.23                 | 0.7            | 136.2                 | 0.93           | 60.0                   | 0.13                 | 511    | ±0.13 |
| 2           | 0.10      | 0.18                 | 0.4            | 153.7                 | 1.89           | 64.6                   | 0.19                 | 865    | ±0.08 |
| 3           | 0.20      | 0.08                 | 1.7            | 306.2                 | 0.42           | 95.7                   | 0.04                 | 337    | ±0.6  |
| 4           | 0.44      | 0.18                 | 1.7            | 201.9                 | 0.40           | 79.0                   | 0.09                 | 395    | ±0.06 |
| 5           | 0.35      | 0.30                 | 0.8            | 113.7                 | 0.85           | 65.0                   |                      |        |       |
| Mean        | 0.27      | 0.19                 | 1.1            | 182.3                 | 0.90           | 72.9                   | 0.11                 | 527    | ±14.6 |

Vd: volume of distribution, CL$_{tot}$: Total body clearance of piperacillin; AUC$_{INF}$: area under the serum concentration-time curve for an infinite time; $k_{el}$: elimination rate constant; AUC$_{HDF}$: area under the serum concentration-time curve during on-line HDF; CL$_{HDF}$: the piperacillin clearance through on-line HDF; R: amount of piperacillin recovered during the on-line HDF session; SD: standard deviation.