Disposition and Bioavailability of Ceftazidime After Intraperitoneal Administration in Patients Receiving Continuous Ambulatory Peritoneal Dialysis

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ABSTRACT
This study investigated the disposition and bioavailability of ceftazidime when it was given intraperitoneally. Seven patients were given 1 gm of ceftazidime intravenously, and 1 wk later, the same dose was given intraperitoneally. After both intravenous and intraperitoneal dosing, serum and peritoneal dialysate samples were obtained at set time intervals over a 24-h period. High-performance liquid chromatography was used to determine the ceftazidime concentrations in the serum and dialysate samples. Inspection of the concentration versus time data after intraperitoneal dosing demonstrated that serum ceftazidime concentrations reached therapeutic (>8 μg/mL) levels within 30 min and remained in the therapeutic range for the entire 24-h period. Simulation of a variety of ceftazidime dosing regimens using the mean pharmacokinetic parameters from this population of patients suggests that a regimen of 1.5 gm administered intraperitoneally every 24 h produces trough serum drug concentrations (approximately 40 μg/mL) similar to those achieved with a standard regimen of 1.0 gm given intravenously every 24 h in patients undergoing continuous ambulatory peritoneal dialysis. It was concluded that the intraperitoneal dosing of ceftazidime in these patients is an equally effective and a more convenient alternative to its administration.

Key Words: Ceftazidime, peritoneal dialysis, pharmacokinetics

Ceftazidime is a bacterioidal third-generation cephalosporin with broad Gram-negative coverage. It is often used as a single agent for the treatment of serious Gram-negative infections and is especially effective in Pseudomonas aeruginosa infections. Ceftazidime-sensitive organisms are generally observed to have a minimum inhibitory concentration of 2 μg/mL (1).

The pharmacokinetics of ceftazidime have been studied in healthy subjects and in patients with ESRD. Ceftazidime is eliminated almost entirely by renal clearance and undergoes very little hepatic degradation in healthy individuals (2). The serum half-life of ceftazidime administered intravenously (iv) is greatly prolonged in the setting of renal failure (3). Ceftazidime is generally administered iv in patients undergoing continuous ambulatory peritoneal dialysis (CAPD), with a usual dosing regimen of 1 g every 24 h. Considering the ever-increasing cost of inpatient medical therapy, we wanted to test the feasibility of the intraperitoneal (ip) administration of ceftazidime in CAPD patients. Intraperitoneal administration can be conducted in the outpatient setting, thus greatly reducing medical costs. Our study was performed with two interests in mind: (1) to determine the pharmacokinetics and bioavailability of ip-administered ceftazidime in CAPD patients, and (2) to determine whether ip dosing could achieve clinically useful serum levels in these patients.

MATERIALS AND METHODS

The study was performed in seven patients with chronic renal failure who were undergoing maintenance peritoneal dialysis. Selected clinical characteristics of the study population are presented in Table 1. Each patient was admitted on two separate occasions to the Clinical Research Center of the University of Virginia Hospital, first for iv dosing and then 1 wk later for ip dosing of ceftazidime. In the intravenous dosing phase of the study, each patient received 1 gm of the drug infused in 50 mL of normal saline over 30 min. Blood samples for the determination of concentrations of ceftazidime were then drawn at 30, 60, 120, 360, 720, and 1440 min after the completion of drug infusion. In the ip dosing phase of the study, 2 L of 2.5% dextrose peritoneal dialysis fluid were allowed to drain, and were then replaced with 2 L of fresh dialysis fluid containing 1 g of ceftazidime. Blood sampling followed the same scheme used in the iv phase of the study, beginning 30 min after the onset of infusion of the ceftazidime-containing dialysis fluid into the peritoneal cavity. In both the iv and ip phases of the study, dosing of ceftazidime was initiated after completing a 2-L exchange of dialysis fluid, and 2-L exchanges were continued on an every-6-h schedule thereafter. The drain volume and the concentration of ceftazidime in the dialysate were measured at the end of each dwell.

Samples of dialysate fluid and serum were kept at −40°C before processing. The concentration of ceftazidime in the samples were assayed by a high-pressure liquid chromatog-
TABLE 1. Clinical characteristics of individual patients undergoing continuous ambulatory peritoneal dialysis (CAPD)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Body Weight (kg)</th>
<th>Cr Cl&lt;sup&gt;a&lt;/sup&gt; (mL/min)</th>
<th>Primary Diagnosis</th>
<th>Duration of CAPD (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>63</td>
<td>84</td>
<td>2</td>
<td>Type II Diabetes</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>67</td>
<td>93</td>
<td>0</td>
<td>Hypertension</td>
<td>17</td>
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<tr>
<td>3</td>
<td>F</td>
<td>58</td>
<td>123</td>
<td>3</td>
<td>Type II Diabetes</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>71</td>
<td>98</td>
<td>1</td>
<td>Atheroemboli</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>52</td>
<td>104</td>
<td>2</td>
<td>Type II Diabetes</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>56</td>
<td>91</td>
<td>8</td>
<td>Type II Diabetes</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>51</td>
<td>89</td>
<td>3</td>
<td>Hypertension</td>
<td>15</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>60</td>
<td>97</td>
<td>3</td>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cr Cl, creatinine clearance.

Pharmacokinetic Analysis

Initial pharmacokinetic analysis was performed using noncompartmental methods. The area under the concentration versus time curve (AUC) was obtained using the trapezoidal rule. The elimination rate constant (k<sub>e</sub>) was determined from the slope of the last three drug concentrations (360, 720, and 1440 min) plotted as their logarithms versus time. The bioavailability (F) of ceftazidime given ip was calculated by dividing the ip AUC into the iv AUC.

Determination of an appropriate compartmental model to describe the drug's pharmacokinetics after iv dosing was performed by curve-stripping, using the method of residuals (5). This analysis generated estimates of microscopic intercompartmental rate constants (k<sub>12</sub>, k<sub>21</sub>), as well as of steady-state volume of distribution (V<sub>ss</sub>), central volume of distribution (V<sub>c</sub>), clearance (CL) and an elimination half-life (t<sub>1/2</sub>). Discrimination between a one- and a two-compartment open linear model relied upon a comparison of the respective sum of the errors squared generated by those two models, corrected for their degrees of freedom. These initial estimates of ceftazidime's pharmacokinetic parameters were then refined using nonlinear least-squares regression analysis (Abbott base Pharmacokinetic Systems, Version 1.0; Abbott Laboratories, Abbott Park, IL). An initial estimate of the first-order absorption rate constant (k<sub>a</sub>) describing the drug's movement from the peritoneum into the systemic circulation was obtained by making the simplifying assumption that a one-compartment model would be adequate to describe the ip data, again using the method of residuals. This estimate of k<sub>a</sub> was then refined by applying nonlinear least-squares regression analysis simultaneously to the iv and ip dosing and concentration data for each patient, in the context of a two-compartment open linear model.

RESULTS

There were no noted adverse side effects observed after either iv or ip administration of ceftazidime.

The plasma ceftazidime concentration (mean with standard deviation [SD]) versus time profile after its intravenous administration is shown in Figure 1, and the same profile after ip administration is shown in Figure 2. Notably, therapeutic plasma concentrations (>2 µg/mL) of ceftazidime were achieved within 30 min of the introduction of 1 g of the drug into the peritoneum, and then remained above the minimum inhibitory concentration for susceptible organisms for the following 24 h. Thirty minutes after ip dosing, the mean plasma ceftazidime concentration was 10.3 µg/mL; the mean peak concentration of 37.7 µg/mL was
observed at 6 h, and after 24 h the mean plasma concentration was 17.4 µg/mL.

The bioavailability of ceftazidime was found to be good, ranging from 0.63 to 0.80 in this population of patients. The bioavailability of the drug did not appear to be significantly affected by the removal of ceftazidime-containing dialysate after the 6-h dwell time. With the first exchange of peritoneal dialysis fluid, the amount of ceftazidime found in the 2 L drained was only 47 ± 19.4 mg (SD) after iv dosing. Over the 24-h period, only 33.9 ± 16.9 mg (SD) and 66.4 ± 21.1 mg (SD) of ceftazidime were recovered from the drained dialysis fluid after iv and ip dosing, respectively.

When curve-stripping analysis using the method of residuals was applied to the data, a two-compartment open linear model was found to best describe the data, with the following mean parameter values: $V_c = 0.07 \text{ L/kg}$, $CL = 0.00869 \text{ L/h per kg}$, $k_{12} = 1.9/\text{h}$, $k_{21} = 0.456/\text{h}$. Curve-stripping analysis of the iv data yielded an initial estimate for $k_a$. These initial estimates were then refined by nonlinear least-squares analysis of the combined iv and ip data, with the following results (mean ± CV [coefficient of variation]): $V_c = 0.114 \text{ L/kg (47%)}$, $CL = 0.00963 \text{ L/h per kg (21%)}$, $k_{12} = 2.3/\text{h (91%)}$, $k_{21} = 1.82/\text{h (74%)}$, $t_{1/2} = 15.9 \text{h (21%)}$, $V_d = 16.0 \text{ L (18%)}$, $k_a = 0.226 (22\%)$, $F = 0.74 (34\%)$.

**DISCUSSION**

Patients with end-stage renal failure managed with CAPD often have poor iv access because of the many years of repeated phlebotomies and attempts at vascular access for hemodialysis. Thus the ip administration of medications is an attractive alternative to iv therapy in these patients. For example, the ip administration of vancomycin renders adequate serum levels for the treatment of systemic infection (6). We therefore undertook this study to examine the feasibility of delivering ceftazidime by the ip route.

The pharmacokinetics of iv-administered ceftazidime has been studied extensively in healthy subjects and in patients with renal insufficiency. This study examines the pharmacokinetics of ceftazidime administered iv and ip in CAPD patients. The following observations provide further support for the ip delivery of this frequently used antibiotic.

Our initial noncompartment analysis of the concentration versus time data after iv dosing of ceftazidime yielded values for $V_d$, $t_{1/2}$, and CL that conform with previously published results of the drug's pharmacokinetics in patients with GFR < 15 mL/min (3). Similarly, the biexponential concentration versus time decay after iv bolus dosing, which suggests a two-compartment open linear model, has been described previously (2). Given that previous work has shown the drug to be cleared almost entirely by the kidneys, it is unlikely that the decreased AUC associated with ip dosing was a reflection of induction of the drug's hepatic clearance by the iv dose given 1 wk earlier.

Intraperitoneal dosing of ceftazidime was associated with good bioavailability (74%) and rapid absorption, these characteristics being demonstrated by the rapid achievement of therapeutic plasma concentrations and the near-complete removal of the drug from the dialysate after a 6-h dwell time. Moreover, bactericidal plasma ceftazidime concentrations were found in all of the patients 24 h after ip dosing. Hence, all of the requirements for the drug's effective clinical use via the ip route were fulfilled.

Although ip delivery of 1 g of ceftazidime achieved all of these desired clinical end points in each of the patients studied, it must be pointed out that the patient population was small. Therefore, it is possible that a dose of 1 gram ip could either fail to achieve bactericidal plasma ceftazidime concentrations within the first 30 min of its administration, or could fail to maintain such concentrations for the entire 24-h period in a small subset of patients. Hence, we have simulated the results of ip ceftazidime dosing using the pharmacokinetic parameters generated from this study and have compared them with iv dosing (Figure 3). The standard regimen of 1 gram iv every 24 h results in steady-state trough concentrations of approximately 40 µg/mL. To maintain the same steady-state trough concentrations with ip dosing, 1.5 g every 24 h should be delivered and, hence,

Figure 3. Serum ceftazidime concentration over time, simulation of iv and ip doses. Dosing simulation curves were created using Abbottbase Pharmacokinetic Systems, Version 1.0, utilizing pharmacokinetic parameters generated in this study.
Ceftazidime Dosage in CAPD Patients

this is the regimen that we would recommend if this route of administration is chosen.

In conclusion, the iv administration of ceftazidime is safe and effective. It is also a more cost-effective alternative to iv administration, allowing for outpatient antibiotic therapy. We recommend a dosing regimen of 1.5 g iv every 24 h for CAPD patients.

ACKNOWLEDGMENT
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REFERENCES