Pharmacokinetics of Once Daily Intraperitoneal Cefazolin in Continuous Ambulatory Peritoneal Dialysis Patients

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Abstract. This study determined the pharmacokinetic characteristics of once daily intraperitoneal (IP) cefazolin in continuous ambulatory peritoneal dialysis (CAPD) patients. Each of the 10 volunteer CAPD patients without active peritonitis received a single IP dose of 1 g of cefazolin sodium for a 6-h dwell. All patients underwent a fixed CAPD regimen comprising a first 6-h dwell followed by two 3-h dwells and a final 12-h overnight dwell. Blood and dialysate samples were collected at 0, 0.5, 1, 2, 3, 6 (end of first dwell), and 24 h after the administration of IP cefazolin. Any urine produced was collected over the 24-h study period. A validated HPLC method was used to analyze cefazolin in plasma, dialysate, and urine.

The bioavailability was found to be 77.9 ± 3.1%, volume of distribution 0.20 ± 0.05 L/kg, and plasma half-life 39.9 ± 25.4 h. Mean total, renal, and peritoneal clearances were 4.5 ± 2.3, 1.4 ± 1.1, and 3.5 ± 1.8 ml/min, respectively. Mean plasma and dialysate concentrations at 24 h were 42.8 ± 14.3 and 31.8 ± 11.7 mcg/ml, respectively, well above the minimum inhibitory concentrations (MIC) of susceptible organisms. A once daily IP cefazolin dose of 500 mg/L gave desirable pharmacokinetic attributes for use as a suitable alternative to vancomycin for empiric treatment of CAPD-associated peritonitis.

Since the advent of continuous ambulatory peritoneal dialysis (CAPD) as a treatment modality for end-stage renal failure, peritonitis remains one of the major complications of this dialytic method (1–4). The most common organisms implicated in CAPD-associated peritonitis are the Gram-positive organisms, although Gram-negative and fungal infections do occur but to a lesser extent (5–7).

Vancomycin has excellent activity against Gram-positive organisms, and thus is a very useful antibiotic for the empiric therapy for peritonitis. Its unique pharmacokinetic properties have also enabled the use of a very convenient once weekly intraperitoneal (IP) dosing regimen. Excellent cure rates with vancomycin have been well documented (8–11).

However, with the emergence of vancomycin-resistant enterococci strains (12–14), and with the possibility of transferring this resistance to other more pathogenic Gram-positive bacteria (15,16), e.g., Staphylococcus aureus, there is an urgent need to curb the indiscriminate use of vancomycin (17,18). This has prompted the Ad Hoc Advisory Committee for the management of peritonitis to recommend the empiric use of cefazolin or cephalothin together with an aminoglycoside over vancomycin unless resistant strains are encountered (19).

Cefazolin is active against most of the Gram-positive bacterial isolates commonly encountered in CAPD-associated peritonitis (20,21). In the clinical setting, cefazolin has long been used to treat Gram-positive and Gram-negative bacterial infections of the skin and respiratory, biliary, and urinary tracts (22). Tolerance to cefazolin has been excellent with rare occurrences of side effects (23,24). However, there is little information of the pharmacokinetics of intermittent IP cefazolin in CAPD patients. The present study aims to characterize the pharmacokinetics of once-daily cefazolin in volunteer CAPD patients.

Materials and Methods

Study Population

Ten stable, volunteer CAPD patients were recruited for the study. Patients older than 18 yr of age who had been on CAPD for at least 1 mo were selected for the study. Patients were not eligible for the study if they had active peritonitis and/or exit-site infection within the last 2 wk before the study. Patients with reported allergy to penicillins and/or cephalosporins were also not included. Approval from the hospital’s Research and Ethics Committee was obtained before patient recruitment. Informed consent was obtained from all patients before the study.

Treatment Protocol

The study started with the first exchange in the morning. Spent dialysate from the previous night was drained. Each patient received 1 g of cefazolin sodium (Pan Pharma) intraperitoneally. Cefazolin sodium was reconstituted with 2 ml of sterile water for injection before being spiked into a 1.5% dextrose, 2-L bag of dialysate. The bag was shaken to ensure adequate mixing, and the spiked dialysate was infused into the peritoneal cavity over 10 to 15 min. Time 0 was defined as the time immediately after the installation of the dialysate spiked with cefazolin into the peritoneal cavity. Blood samples of 2 ml each were collected in duplicate via an in-dwelling catheter or venipuncture at time 0, 0.5, 1, 2, 3, 6, and 24 h. Ethylenediaminetetraacetic acid-coated Vacutainer tubes were used to collect the blood until processed further. Using a technique described previously (25),
dialysate samples of 10 ml each were collected at the same time intervals.

At the end of 6 h (first dwell), the spent dialysate was drained and a second 2-L bag of fresh dialysate (1.5% dextrose) was introduced into the peritoneal cavity. All patients underwent an initial 6-h (1.5% dextrose) dwell followed by two 3-h (1.5% dextrose) dwells and a final 12-h overnight dwell (4.25% dextrose). The total volume of each bag of spent dialysate was measured and recorded. A 10-ml sample of each bag of spent dialysate was taken and frozen at −80°C until assayed.

Patients with urine production >50 ml/d voided urine just before the start of the study. Urine sample was collected over 24 h and frozen at −80°C until assayed. The total volume of urine produced by the patient was measured and recorded. An aliquot of urine (20 ml) was retained for cefazolin analysis.

**Assay Method**

A validated HPLC method was used to assay cefazolin in plasma, urine, and dialysate (26). The intra- and inter-day coefficients of variation were 2.0 and 2.1%, respectively.

**Pharmacokinetic Calculations**

A monoeponential model was used, because it was assumed that there was no marked distribution phase following IP administration of cefazolin.

The bioavailability (F) was calculated by subtracting the amount of cefazolin remaining in the bag after the first 6-h dwell from the dose of cefazolin administered, since cefazolin is not hepatically metabolized (20) and is stable in peritoneal fluid (27).

The rate constant for the removal of cefazolin from the peritoneal cavity (kpc-cc) was the slope obtained by the linear plot of dialysate concentrations obtained from time 0 to 6 h. The half-life ($t_{1/2pc-cc}$) of drug removal from the peritoneal cavity was calculated as $\ln 2/kpc-cc$. The plasma elimination rate constant (kel) was the slope of the linear plot of plasma concentration obtained by 6- and 24-h plasma samples versus time. The plasma elimination half-life ($t_{1/2el}$) was calculated as $\ln 2/\text{kel}$. The equilibration half-life ($t_{1/2eq}$), defined as the time taken for cefazolin concentration to reach 50% equilibration between plasma and dialysate, was calculated by $\ln 2/\text{kel} + \text{kpc-cc}$.

The total clearance of cefazolin was calculated as follows:

$$\text{CL}_{\text{total}}(\text{L/h}) = F \times \frac{\text{Dose}}{\text{[AUC}_{0-\infty}]_{\text{plasma}}}$$

The plasma area under the curve (AUC) was calculated using the trapezoid rule, starting from 0 to 24 h, and included the extrapolation to infinity ($\infty$) (28). The volume of distribution ($V_d$) was calculated as $\text{CL}_{\text{total}}(\text{L/h})/\text{kel}$.

Renal clearance ($\text{CL}_r$) was calculated by the following formula:

$$\text{CL}_r = \frac{\text{Amount of cefazolin in urine from 0 to 24 h}}{\text{Plasma cefazolin concentration at 12h (extrapolated)} \times 24}$$

The 12-h plasma cefazolin concentration was extrapolated from the concentration versus time profile, assuming first-order pharmacokinetics. The peritoneal clearance ($\text{CL}_p$) was taken as the difference between total clearance and renal clearance of cefazolin. This was compared to the calculated peritoneal clearance using the following equation:

$$\text{CL}_p = \frac{\text{Amount of cefazolin in the 2nd, 3rd and 4th bags of spent dialysate}}{\text{Extrapolated plasma cefazolin concentration at 15 h} \times 18}$$

**Statistical Analyses**

Continuous variables were expressed as mean ± SD. Statistically significant differences between the means of certain parameters were calculated using t test (unpaired).

**Results**

A total of 10 patients (two males) completed the study (six were Chinese, three were Malaysian, and 1 was Indian). The mean age of patients was 59 ± 10 yr. Nonanuric (6) and anuric (4) patients had been on CAPD for an average of 40 ± 17 and 50 ± 32 mo, respectively. The average body weight of these patients was 57 ± 14 kg. The volume of urine production per day ranged from 400 to 1150 ml for nonanuric patients. Cefazolin was well tolerated by all of the patients, and none displayed any signs of adverse effects.

The average bioavailability of IP cefazolin was 77.9 ± 3.1%. The calculated volume of distribution, 0.20 ± 0.05 L/kg,
is within the reported range for cefazolin. Figure 1 provides a representation of the concentration versus time profile of cefazolin in plasma and dialysate after IP administration of cefazolin. In general, plasma concentrations increased by almost two and a half times from the first half-hour after administration (26.7 ± 13.2 mcg/ml) to the end of the first 6-h dwell (64.6 ± 13.3 mcg/ml). There was a decrease in the dialysate concentration from time 0 (458.8 ± 49.9 mcg/ml) to the end of the first 6-h dwell (115.6 ± 41.3 mcg/ml). Mean plasma and dialysate concentrations at 24 h were 42.8 ± 14.3 and 31.8 ± 11.7 mcg/ml, respectively.

Half of the study patients have either high or high-average transport status as determined by the peritoneal equilibration test, while the other patients were all low-average transporters. The average residual renal function as measured using creatinine clearance was 4.83 ± 2.16 ml/min for nonanuric patients. A summary of the pharmacokinetic parameters obtained and the estimated peritoneal clearance are shown in Table 1. The calculated peritoneal clearance ranged from 95 to 105% of that estimated by assuming that it was the difference between total clearance and renal clearance. Peritoneal clearance (3.8 ± 1.1 ml/min) accounted for approximately 69% of total body clearance of cefazolin (5.5 ± 1.3 ml/min) in six nonanuric patients, while renal clearance (1.7 ± 0.9 ml/min) accounted for 31% of the total body clearance of cefazolin. Urine production per 24 h varied among the nonanuric patients (795 ± 307 ml).

### Discussion

The mean bioavailability of cefazolin ($F = 77.9 ± 3.1\%$) was relatively high, suggesting that rapid systemic absorption of cefazolin occurs after IP administration of cefazolin. The low molecular weight of cefazolin (molecular weight, 454.5) facilitates its transport across the pores of the peritoneal capillaries. It is expected that bioavailability will increase in the presence of active peritonitis. This increased bioavailability would allow greater absorption of antibiotics even with a shorter dwell time. The enhanced absorption of aminoglycosides (29-30), vancomycin (31), and several $\beta$-lactam antibiotics (32), including cefazolin (32), during active peritonitis have been reported previously. The transport status of the patients did not seem to affect the bioavailability, clearance, and other pharmacokinetic parameters.

The mean apparent volume of distribution of cefazolin was determined to be 0.20 ± 0.05 L/kg. This is in agreement with the reported volume of distribution range, 0.14 to 0.22 L/kg, for cefazolin determined in end-stage renal failure patients (32-38). The rapid removal from the peritoneum is a consequence of cefazolin’s pharmacokinetic parameters, i.e., large volume of distribution and high protein binding. The contrast between the small peritoneum volume and the large systemic volume of distribution of cefazolin leads to a pronounced concentration gradient between the peritoneal cavity and the systemic circulation.

Cefazolin is 80% plasma protein bound (20), while the protein binding in dialysate is insignificant. This discrepancy in protein binding enhances the apparent unidirectional transport of cefazolin into the plasma. This phenomenon observed with cefazolin has also been reported by Bunke et al. (38). After the first exchange, the plasma cefazolin then acts as a reservoir for the transfer of cefazolin back into the peritoneal cavity in subsequent exchanges. Plasma concentrations still exceeded dialysate concentrations at the end of the second, third, and final exchanges.

Anuric patients produced higher plasma concentrations at 6 h (75.2 ± 7.1 mcg/ml) and 24 h (60.3 ± 5.5 mcg/ml) after IP administration of cefazolin compared to nonanuric patients. The nonanuric patients had residual creatinine clearance ranging from 1.5 to 7 ml/min. Plasma concentrations at 6 and 24 h exceeded dialysate concentrations at the end of the second, third, and final exchanges.

### Table 1. Pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Patient</th>
<th>$F$ (%)</th>
<th>kpc-cc (h$^{-1}$)</th>
<th>kel (h$^{-1}$)</th>
<th>$t_{1/2pc}$ (h)</th>
<th>$t_{1/2el}$ (h)</th>
<th>$t_{1/2eq}$ (h)</th>
<th>$V_d$ (L/kg)</th>
<th>$CL_{total}$ (ml/min)</th>
<th>$CL_r$ (ml/min)</th>
<th>$CL_p$ (ml/min)</th>
<th>Weight (kg)</th>
<th>Transport Status</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>74.4</td>
<td>0.203</td>
<td>3.41</td>
<td>5.49</td>
<td>44.42</td>
<td>4.89</td>
<td>0.18</td>
<td>2.17</td>
<td>0</td>
<td>2.17</td>
<td>41.1</td>
<td>LA</td>
</tr>
<tr>
<td>2</td>
<td>70.4</td>
<td>0.126</td>
<td>0.016</td>
<td>2.88</td>
<td>26.45</td>
<td>2.11</td>
<td>0.29</td>
<td>7.48</td>
<td>2.82</td>
<td>4.66</td>
<td>46.0</td>
<td>HI</td>
</tr>
<tr>
<td>3</td>
<td>79.3</td>
<td>0.303</td>
<td>0.026</td>
<td>2.42</td>
<td>44.03</td>
<td>2.29</td>
<td>0.26</td>
<td>3.95</td>
<td>1.11</td>
<td>2.84</td>
<td>60.0</td>
<td>LA</td>
</tr>
<tr>
<td>4</td>
<td>79.7</td>
<td>0.286</td>
<td>0.016</td>
<td>2.60</td>
<td>80.00</td>
<td>2.52</td>
<td>0.19</td>
<td>1.38</td>
<td>0</td>
<td>1.38</td>
<td>51.6</td>
<td>LA</td>
</tr>
<tr>
<td>5</td>
<td>79.8</td>
<td>0.266</td>
<td>0.009</td>
<td>2.71</td>
<td>78.94</td>
<td>2.62</td>
<td>0.16</td>
<td>1.75</td>
<td>0</td>
<td>1.75</td>
<td>75.4</td>
<td>LA</td>
</tr>
<tr>
<td>6</td>
<td>80.0</td>
<td>0.256</td>
<td>0.009</td>
<td>2.75</td>
<td>17.92</td>
<td>2.39</td>
<td>0.23</td>
<td>6.02</td>
<td>1.20</td>
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<td>41.0</td>
<td>HA</td>
</tr>
<tr>
<td>7</td>
<td>78.9</td>
<td>0.252</td>
<td>0.039</td>
<td>2.75</td>
<td>17.92</td>
<td>2.39</td>
<td>0.23</td>
<td>6.02</td>
<td>1.20</td>
<td>4.83</td>
<td>41.0</td>
<td>HA</td>
</tr>
<tr>
<td>8</td>
<td>78.1</td>
<td>0.289</td>
<td>0.025</td>
<td>2.70</td>
<td>27.94</td>
<td>2.21</td>
<td>0.23</td>
<td>5.08</td>
<td>2.62</td>
<td>2.45</td>
<td>54.2</td>
<td>HA</td>
</tr>
<tr>
<td>9</td>
<td>80.0</td>
<td>0.233</td>
<td>0.026</td>
<td>2.97</td>
<td>26.25</td>
<td>2.67</td>
<td>0.14</td>
<td>5.16</td>
<td>0.85</td>
<td>4.31</td>
<td>83.1</td>
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</tr>
<tr>
<td>10</td>
<td>78.0</td>
<td>0.267</td>
<td>0.053</td>
<td>2.59</td>
<td>13.09</td>
<td>2.16</td>
<td>0.13</td>
<td>7.06</td>
<td>0</td>
<td>7.06</td>
<td>64.0</td>
<td>LA</td>
</tr>
<tr>
<td>Mean</td>
<td>77.9</td>
<td>0.248</td>
<td>0.024</td>
<td>2.96</td>
<td>39.89</td>
<td>2.65</td>
<td>0.20</td>
<td>4.45</td>
<td>1.72</td>
<td>3.48</td>
<td>57.0</td>
<td>LA</td>
</tr>
<tr>
<td>SD</td>
<td>3.1</td>
<td>3.149</td>
<td>0.014</td>
<td>0.94</td>
<td>25.35</td>
<td>0.86</td>
<td>0.05</td>
<td>2.28</td>
<td>0.92</td>
<td>1.83</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

$F$, bioavailability; kpc-cc, rate constant for the removal of cefazolin from peritoneal cavity; kel, plasma elimination rate constant; $t_{1/2pc}$, elimination half-life of cefazolin in peritoneal cavity; $t_{1/2el}$, plasma elimination half-life; $t_{1/2eq}$, equilibration half-life; $V_d$, apparent volume of distribution of cefazolin; $CL_{total}$, $CL_r$, and $CL_p$, total body, renal, and peritoneal clearances, respectively; LA, low-average; HA, high-average; HI, high.

AQ1—Au: Units shown correctly?
for nonanuric patients were 60.9 ± 15.0 and 34.8 ± 4.7 mcg/ml, respectively. The dialysate concentrations for anuric and nonanuric patients at 24 h were 33.3 ± 3.4 and 30.9 ± 15.4 mcg/ml, respectively. All of these levels were above the MIC of susceptible organisms for both anuric and nonanuric patients. For patients with serum creatinine >7 ml/min, higher doses or more frequent dosing of cefazolin may be more appropriate to ensure therapeutic plasma and dialysate cefazo-

lin concentrations.

The difference in the total clearance of cefazolin between nonanuric and anuric patients (5.5 ± 1.3 ml/min versus 3.1 ± 2.7 ml/min, P < 0.017) was statistically significant. The peritoneal clearances of anuric patients were slightly lower (3.1 ± 2.7 ml/min) than that of nonanuric patients (3.8 ± 1.1 ml/min). Without renal clearance, cefazolin plasma elimination half-life was longer for anuric patients (54.1 ± 32.0 h) compared to that obtained from nonanuric patients (28.5 ± 9.5 h).

Anuric patients had a smaller volume of distribution (mean 0.16 ± 0.03 L/kg) compared to nonanuric patients (mean 0.22 ± 0.05 L/kg), although not statistically significant. This could not be explained by the difference in ideal body weight of patients. All of the patients were below their ideal body weight except one anuric patient. A bigger study population would be helpful to establish whether this observation is truly significant.

Cefazolin given as a once daily IP dose of 1 g (500 mg/L) is more convenient for patients and caregivers compared with continuous dosing. Once daily dosing of cefazolin was thought to predispose the patient to relapsing peritonitis because of subtherapeutic levels (39). Despite this, recent studies have revealed that once daily dosing of cefazolin is efficacious at eradicating microbes with intermediary susceptibility to it (40–42). Furthermore, the pharmacokinetics of cefazolin unveiled in our study have confirmed that plasma concentrations at 24 h exceed the MIC of susceptible microbes.

The combination of cefazolin (500 mg/L) and gentamicin (0.6 mg/kg) given once daily as empiric therapy to treat CAPD peritonitis is a promising alternative. In fact, this combination has demonstrated synergistic effect in the treatment of peritonitis (40–42). In institutions where resistance to cefazolin is low, cefazolin would be an excellent alternative empiric treatment for CAPD peritonitis. However, a clinical dilemma may exist in institutions where resistance to cefazolin is high. Two recent efficacy studies (43,44) carried out in hemodialysis patients found that cefazolin was as efficacious as vancomycin when used as empiric treatment of clinically significant infections. Future studies should address the comparative efficacy of intermittent IP vancomycin versus cefazolin in the treatment of peritonitis in CAPD patients.

In conclusion, 1 g of IP cefazolin given once daily over a 6-h dwell maintains therapeutic plasma and dialysate levels, even in those with some residual renal function (creatinine clearance <7ml/min), and appears to be safe for the empiric treatment of peritonitis in CAPD patients. It should be considered as the first line therapy over vancomycin to reduce the incidence of vancomycin-resistant enterococcus and Staphylococcus au-

reus.

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