Reevaluation of Ceftazidime Dosing Recommendations in Patients on Continuous Ambulatory Peritoneal Dialysis

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While intraperitoneal (i.p.) ceftazidime is commonly used to treat continuous ambulatory peritoneal dialysis (CAPD)-related infections, the ability of i.p. regimens to achieve critical pharmacodynamic targets in both blood and dialysate has not been reported. To understand the pharmacodynamic profile of ceftazidime during CAPD, data were obtained from a single-dose pharmacokinetic (PK) i.p. ceftazidime study that included 10 CAPD patients who received i.p. ceftazidime at 15 mg/kg of body weight. The probability of target attainment (concentrations maintained above the MIC for >60% of the dosing interval [60% \( T > \text{MIC} \)]) was determined for six simulated regimens. A 3-compartment model with each dialysis dwell modeled as a separate differential equation was fit to ceftazidime concentrations using BigNPAG. Embedded with the final PK model, serum and dialysate concentration-time profiles of ceftazidime at 1, 1.5, and 2 g i.p. every 24 h (q24h) to q48h were simulated using ADAPT 5. The mean population pharmacokinetic parameters were as follows: apparent volume of the central compartment (\( V_c \)), 7.57 liter; apparent volume of the peritoneal cavity (\( V_{pd} \)), 2.44 liter; clearance from the central compartment (\( CL \)), 0.379 liter/h; intercompartmental transfer rate constants (first order) between the central and peripheral compartments (\( k_{12} \) and \( k_{21} \)), 4.66 and 4.88 h\(^{-1} \), respectively; and intercompartmental transfer rate constants (first order) between the central and peritoneal compartments (\( k_{13} \) and \( k_{31} \)), 0.111 and 0.227 h\(^{-1} \), respectively. In serum, the probability of target attainment for MICs of \( \leq 8 \, \text{mg/liter} \) exceeded 90% for 1.5 to 2 g i.p. q24h to q48h. However, no tested regimen provided adequate dialysate exposure at MICs of \( \geq 8 \, \text{mg/liter} \) on day 1 without the use of a 3-g loading dose (post hoc analysis). On day 2, 1.5 to 2 g i.p. q24h or 2 g i.p. q48h provided adequate exposure in the peritoneal cavity. These results should be validated in the presence of infection. Ceftazidime i.p. at 1.5 or 2 g q24h to q48h is recommended for nonperitoneal infections. For peritonitis, a 3-g load with maintenance dosing of 1 to 2 g i.p. q24h or 2 g i.p. q48h is recommended.

Peritoneal dialysis (PD) is the life-sustaining treatment used by nearly 30,000 Americans with end-stage kidney disease (1). Infection remains an important complication for the PD population and contributes significantly to hospitalizations, mortality, and dialysis modality failure (1). All-cause infections account for nearly 600 hospital admissions per 1,000 PD patient-years, and the risk for infection-related hospitalization is higher among patients on PD than for those on hemodialysis (1, 2). While infection is the most common cause of death among PD patients, infectious disease processes likely also contribute to cardiovascular events, the most common cause of mortality (1, 3). Despite the clear need for clinically sound antibiotic dosing recommendations in the PD patient population, the data in the literature in this area are often limited or conflicting.

Empirical antibiotic therapy for patients on PD with suspected or documented infections should provide a broad spectrum of coverage for both Gram-positive and Gram-negative organisms (4). Although aminoglycosides remain important options for coverage of Gram-negative organisms, concerns of ototoxicity or loss of residual kidney function exist, and an adequate pharmacodynamic profile (i.e., high peak concentrations) is difficult to achieve safely given the degree of drug accumulation in patients with compromised renal function (4, 5). For these reasons, beta-lactam antibiotics, such as ceftazidime, with extensive coverage of Gram-negative pathogens are preferred (4, 6). To date, multiple pharmacokinetic (PK) studies of intraperitoneal (i.p.) ceftazidime have been conducted and have recommended a range of dosing schemes with various antibiotic dwell times, weight-based versus fixed doses, dosing amounts, continuous versus intermittent dosing, and differing frequencies of administration (7–16). On the basis of data from these studies, the current guideline for peritoneal-dialysis-related infections suggests using 1 or 1.5 g of ceftazidime administered via the i.p. route every 24 h (q24h) for the treatment of peritonitis (4). This recommendation varies from the approved ceftazidime labeling by the U.S. Food and Drug Administration (FDA), which recommends 250 mg in 2 liters of peritoneal dialysate for i.p. administration (6).

Although PK data exist on i.p. administration of ceftazidime, previous studies have not evaluated the ability of the suggested regimens to achieve the pharmacodynamic targets associated with a positive outcome (i.e., free drug concentrations above the MIC for at least 60% of the dosing interval) in blood and the peritoneal cavity (17, 18). Therefore, it remains unclear what i.p. regimen is optimal for peritonitis over the range of MICs encountered in clinical practice. It is also unclear whether the suggested i.p. regimens provide adequate serum concentrations to treat nonperitoneal systemic infections. To address these gaps in the literature, the objective of this study was to characterize the pharmacody-
namic profiles of currently used i.p. ceftazidime dosing schemes in both serum and the peritoneal cavity.

MATERIALS AND METHODS

Study design and population. Data were obtained from a previously conducted prospective, single-dose PK study (13). The study included adult (≥18 years) noninfected patients on a stable continuous ambulatory PD (CAPD) regimen for at least 2 months. Patients were excluded if they had peritonitis or had received antibiotics within the previous 4 weeks, had an allergy to cephalosporin drugs, or had a documented anaphylactic reaction to beta-lactam medications. Ten patients (four women and six men) were studied, four of whom had anuria. The mean clinical characteristics were as follows: age, 48.2 ± 14.2 years (mean ± standard deviation); weight, 91.3 ± 21.4 kg; body mass index, 30.8 ± 6.9 kg/m²; and time on dialysis, 25.3 ± 16.6 months. The mean ceftazidime dose administered was 1,378.5 ± 316 mg.

Study procedure. Eligible patients received a standardized CAPD prescription of fourfold daily exchanges with 1.5% dextrose dialysate for the first and fourth daily dwells and 2.5% dextrose dialysate during the second and third dwell periods. The daily dwells were 6 h, 4 h, 6 h, and 8 h, respectively. Ceftazidime at 15 mg/kg of body weight was added to a 2-liter dialysate bag and administered during the first daily dwell for 6 h in duration. Blood and dialysate samples collected at 0.5, 1, 2, 3, 6, and 24 h following drug administration were used for the current analysis (13).

Data analysis. As we have previously described, a three-compartment model with zero-order infusion and first-order intercompartmental transfer and elimination was fit to the data using the Big NonParametric Adaptive Grid with adaptive γ (BigNPAG) software program (19–21). In this model, each exchange was included as a separate differential equation in the structural model.

The following differential equations were used to characterize the PK profile of i.v. administration of ceftazidime: \( \frac{dX_1}{dt} = -(k_{12} + CL/V + k_{13}R_1)V + k_{21}X_2 + k_{31}X_3 + k_{31}X_3R_1 + k_{32}X_2R_1 + k_{31}X_3R_2 + k_{31}X_3R_3 + \frac{k_{31}X_2R_3}{R_2}, \)
\( \frac{dX_2}{dt} = k_{31}X_1 + k_{31}X_2, \)
\( \frac{dX_3}{dt} = R_1 + k_{31}X_3R_1 - k_{31}X_3R_2, \)
\( \frac{dX_1}{dt} = k_{13}X_1R_1 - k_{13}X_1R_2 + \frac{k_{13}X_1R_3}{R_2} \)
\( X_1 \) is the amount of ceftazidime in the central compartment; \( X_2 \) is the amount of ceftazidime in the peripheral compartment; \( X_3 \) is the amount of ceftazidime in the peritoneal cavity during the first PD dwell; \( X_{21} \) is the amount of ceftazidime in the peritoneal cavity during the second dwell; \( X_3 \) is the amount of ceftazidime in the peritoneal cavity during the third dwell; \( X_{60} \) is the amount of ceftazidime in the peritoneal cavity during the fourth dwell; \( CL \) is the non-dialytic clearance from the central compartment (liters per h); \( V \) is the apparent volume of the central compartment (liters); \( k_{12} \) and \( k_{31} \) are the first-order intercompartmental transfer rate constants between the central and peripheral compartments (h⁻¹); \( k_{13} \) and \( k_{32} \) are the first-order intercompartmental transfer rate constants between the central and peritoneal compartments (h⁻¹); \( R_1 \) is the time-delimited zero-order input rate for ceftazidime (piece-wise input function) into the peritoneal cavity (mg per h); and \( R_2 \) to \( R_6 \) are the rate constants for the first through fourth dwells, respectively, constrained to 0 (dwell turned off) or 1 (dwell turned on).

For all models, the inverse of the estimated assay variance was used as the first estimate for weighting. Weighting was accomplished with the assumption that the total observation variance was proportional to the assay variance and was determined on a between-day basis. The analysis was performed with adaptive lambda, a scalar that adds the polynomial described above and is optimized with each cycle to produce the best approximation to the homoscedastic assumption. Lambda is an overall measure of all the other sources of intraindividual variability besides the assay error. In this way, one can calculate how much of the total variance is due to the assay variance and how much is due to the remaining overall environmental variance (22, 23).


Monte Carlo simulation. The mean parameter vector and major diagonal covariance matrix from the population PK model were included in Subroutine PRIOR for the ADAPT 5 program package (25). The population simulation without process noise option was used. A 5,000-subject Monte Carlo simulation was performed for the following six ceftazidime regimens: 1 g i.p. q24h, 1 g i.p. q48h, 1.5 g i.p. q24h, 1.5 g i.p. q48h, 2 g i.p. q24h, and 2 g i.p. q48h.

Normal and log-normal distributions were considered for each parameter in the final PK model used in the simulations. The selected distribution of the PK parameters used in the simulations was based on the ability of the normal versus log-normal distribution to recreate the original mean parameter values and corresponding standard deviations from the population analyses. The parameter values from the optimal distributions were used to generate serum concentration-time curves for each dosing regimen in both the central compartment and the peritoneal cavity. Protein binding was assumed to be 10% in the serum (6). Ceftazidime found in the peritoneal cavity was assumed to be free drug, since the extent of protein binding in this compartment is unknown.

The pharmacodynamic target selected for analyses was the ceftazidime concentration above the MIC for at least 60% of the dosing interval (60% T > MIC) (17, 18). The probability of target attainment (PTA) (i.e., the fraction of simulated subjects whose free ceftazidime concentration remained in excess of the MIC for at least 60% of the dosing interval) was calculated for each regimen for MICs of 0.25 mg/liter to 16 mg/liter in the (i) serum (central compartment) and (ii) peritoneal cavity. According to the Clinical and Laboratory Standards Institute (CLSI) breakpoints, Enterobacteriaceae are considered susceptible to ceftazidime at MICs of ≤4 mg/liter, and non-lactose-fermenting Gram-negative rods, such as Pseudomonas aeruginosa, are susceptible at MICs of ≤8 mg/liter (26). Three windows of time were evaluated for PTA, 0 to 24 h (i.e., day 1), 24 to 48 h (i.e., day 2), and 0 to 48 h (for q48h regimens only). For every-other-day dosing schemes, it is unknown which interval is most appropriate to conduct PTA analyses (i.e., to examine PTA during each 24-h interval or over the entire 48-h dosing interval). For this reason, PTA analyses were conducted for partitioned daily time intervals (i.e., 0 to 24 h and 24 to 48 h), as well as over the entire dosing interval (0 to 48 h). For treatment of peritonitis, regimens were considered acceptable if they achieved at least 90% PTA at target MICs in both the central compartment and the peritoneal cavity. Regimens were considered acceptable for nonperitoneal infection if they achieved at least 90% PTA at target MICs in the central compartment.

The Monte Carlo simulation was also used to evaluate the predictive performance of the population pharmacokinetic model. Please note that a variety of doses were administered to different patients, as the original study was dosed on a 15-mg/kg basis (13). Since the patients received different doses, we simulated the average dose (1.400 mg) received during the original PK study in the study in serum and the peritoneal cavity using the mean parameter vector values and then dispersed the patients’ data points around the simulated points. The fidelity with which the concentration-time curves mirrored the raw data was assessed by visual inspection.

RESULTS

Population PK model. The overall model fit to the data was good. The mean weighted errors, a measure of bias, for observed versus predicted ceftazidime concentrations were −0.04, −0.17, and
0.041 mg/liter for serum, peritoneal cavity (first dwell), and peritoneal cavity (fourth dwell), respectively. The precision, measured using bias-adjusted mean weighted squared error, was 0.47, 1.85, and 0.018 mg/liter (2) for the serum, peritoneal cavity (first dwell), and peritoneal cavity (fourth dwell) concentrations, respectively.

The observed versus predicted plots for serum and dialysate after the Bayesian step showed slopes and intercepts close to the ideal values of 1.0 and 0.0, respectively (Fig. 1). The coefficients of de-

**FIG 1** Observed versus predicted plots for serum concentrations (A) and peritoneal cavity concentrations during dwell 1 (B) and dwell 4 (C).
termination ($r^2$) were $\geq$0.94 for all outputs, and the measures of bias and precision were acceptable. The population PK model parameter estimates for ceftazidime are provided in Table 1. The $\varepsilon$-shrinkage estimates for clearance, volume of distribution in the central compartment, and volume of distribution in the peritoneal compartment were less than 0.05 in all cases. The simulated serum and peritoneal cavity concentrations for 1,400 mg i.p. ceftazidime are shown in Fig. 2. The raw data points from study subjects are generally evenly dispersed around the simulated concentration-time curves. Most importantly, as ceftazidime is a characteristic $T > MIC$ antibiotic, the ceftazidime concentrations at the midpoint and end of the dosing intervals were well captured around the central tendency.

**Probability of PTA analyses.** Figure 3 shows the pharmacodynamic target attainment (PTA) for each regimen in both the peritoneal and central compartment during the first day (from 0 to 24 h) following i.p. dose administration. In the peritoneal cavity, no regimen provided adequate drug exposure during the first 24 h for organisms with a MIC of $\leq 4$ mg/liter. In the central compartment, the 1.5-g and 2-g doses but not the 1-g dose provided adequate coverage for all susceptible organisms (MIC $\leq 8$ mg/liter) during day 1. No regimen was acceptable at a MIC of 16 mg/liter, which is outside the CLSI susceptibility range.

On day 2, a second dose was simulated for the tested regimens of 1 g q24h, 1.5 g q24h, and 2 g q24h. The results of the PTA analyses for each of these regimens during the second treatment day (24 to 48 h) are depicted in Fig. 4. During day 2, 1.5 and 2 g q24h provided acceptable drug exposure in the peritoneal cavity at MICs of $\leq 8$ mg/liter. All q24h regimens (i.e., 1 to 2 g q24h) yielded PTA of $>90\%$ for nonperitoneal infections across the range of MICs evaluated.

**TABLE 1 Population pharmacokinetic parameter estimates**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value ± SD</th>
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<tbody>
<tr>
<td>$V_c$</td>
<td>7.57 ± 3.58 liters</td>
</tr>
<tr>
<td>CL</td>
<td>0.379 ± 0.198 liters/h</td>
</tr>
<tr>
<td>$k_{12}$</td>
<td>4.66 ± 3.77 h$^{-1}$</td>
</tr>
<tr>
<td>$k_{21}$</td>
<td>4.88 ± 6.43 h$^{-1}$</td>
</tr>
<tr>
<td>$k_{13}$</td>
<td>0.111 ± 0.132 h$^{-1}$</td>
</tr>
<tr>
<td>$k_{31}$</td>
<td>0.227 ± 0.0548 h$^{-1}$</td>
</tr>
<tr>
<td>$V_{pd}$</td>
<td>2.44 ± 0.675 liters</td>
</tr>
</tbody>
</table>

$V_c$, apparent volume of the central compartment; CL, nondialytic clearance from the central compartment; $k_{12}$, $k_{31}$, intercompartmental transfer rate constants (first order) between the central and peripheral compartments; $k_{13}$, $k_{32}$, intercompartmental transfer rate constants (first order) between the central and peritoneal compartments; $V_{pd}$, apparent volume of the peritoneal cavity.

FIG 2 Serum (A) and peritoneal (B) ceftazidime concentration versus time profiles.
The PTA analyses for every-other-day dosing schemes (i.e., 1 g q48h, 1.5 g q48h, and 2 g q48h) are depicted in Fig. 5 and 6. Figure 5 shows the PTA analyses for the second day (24 to 48 h) for each q48h regimen. On day 2, only 2 g q48h was highly likely to achieve the pharmacodynamic target in the peritoneal cavity over the range of MICs up to 8 mg/liter. For nonperitoneal infections, 1 to 2 g q48h provided adequate drug exposure in the central compartment for MICs of 8 mg/liter or less during the second day. The PTA analysis for every-other-day dosing regimens over the entire 2-day dosing interval (from 0 to 48 h) is shown in Fig. 6. No regimen provided adequate concentrations for peritonitis at a MIC of 8 mg/liter. However, nonperitoneal infection was adequately covered by 1.5 and 2 g q48h at MICs of up to 8 mg/liter.

DISCUSSION

Our understanding of ceftazidime’s exposure-response relationships has advanced considerably since its U.S. FDA approval in 1985 (17, 18). This, combined with evolving susceptibility patterns among key Gram-negative pathogens, highlights the need for periodic examination of the appropriateness of recommended ceftazidime dosing schemes among patients receiving PD. Effective treatment of PD-related peritonitis is critical to prevent PD modality failure, as well as to avoid hospitalizations and infection-related morbidities. Furthermore, systematic evaluation of dosing schemes for patients receiving dialysis is of paramount importance since the end-stage kidney disease population is typically among the first to develop antibiotic resistance (27–29). Given the low number of antimicrobial agents in the pipeline with activity against key Gram-negative organisms, it is critical to confirm the continued adequacy of commonly used antibiotic regimens.

There are several important considerations when evaluating the appropriateness of an antibiotic dosing scheme for patients on PD. First, interpatient variability in exposure profiles within the patient population for a given drug regimen must be considered. Second, there has to be an understanding of the pharmacodynamic targets associated with optimal response. Third, an assessment of a regimen’s ability to achieve this pharmacodynamic target at the site of infection must be conducted. For infections involving the peritoneal membrane, this requires evaluation of antibiotic concentrations in the peritoneal cavity, as well as the
bloodstream. Fourth, knowledge of the likely pathogens and associated susceptibility patterns is needed.

With cognizance of these issues, we used population PK modeling and Monte Carlo simulation to evaluate i.p. ceftazidime administration in patients on CAPD. This is a well-accepted technique to understand the variability of exposure profiles likely to be observed among a patient population and estimate the probability that regimens achieve adequate drug exposure in both the peritoneal cavity and bloodstream over the MIC range encountered in clinical practice. Overall, we found that 1.5 to 2 g of ceftazidime i.p. every 24 or 48 h was appropriate for treatment of nonperitoneal infections in the central compartment. These regimens were associated with a greater than 90% probability of achieving 60% T/MIC for MICs of up to 8 mg/liter in the serum. This range of MICs represents the susceptibility range for many Gram-negative organisms, including *Enterobacteriaceae* and *Pseudomonas*.

Our findings in the peritoneal cavity were not as straightforward. Despite intraperitoneal administration, drug distribution from the peritoneal cavity into the central and peripheral compartments resulted in lower drug exposures in the peritoneal cavity, particularly after the first exchange on the first day of therapy. As such, no regimen provided adequate exposure at a MIC of 8 mg/liter during the first 24 h. Given the importance of early appropriate therapy, this finding has important implications for clinical practice. Current clinical practice guidelines recommend providing empirical therapy that includes coverage for *Pseudomonas aeruginosa* when peritonitis is suspected (4). Since the CLSI susceptibility breakpoint for non-lactose-fermenting Gram-negative bacteria like *Pseudomonas aeruginosa* is 8 mg/liter, ceftazidime doses of 1 to 2 g i.p. cannot be recommended for peritoneal infections (26). In a post hoc analysis (data not shown), we found that a 3-g i.p. loading dose of ceftazidime was required to achieve a >90% probability of achieving 60% T > MIC in the peritoneal cavity at a MIC of 8 mg/liter during the first 24 h. Following this loading dose, 1 g q24h provided adequate exposure in the peritoneal cavity during day 2. Therefore, subsequent to a 3-g i.p. loading dose, 1 to 2 g i.p. q24h or 2 g q48 h may be given as maintenance dosing to provide adequate drug exposure. Although ceftazidime has a wide therapeutic window, neurologic complications have been reported at moderate doses (e.g., 2 g daily) in patients with kidney disease (30). Therefore, patients receiving a loading dose should be closely monitored for neurologic complications, principally confusion and myoclonus (30). The decision to use daily or every-other-day dosing should be driven by clinician and patient preferences, and the severity of infection. Daily i.p. dosing offers a consistent daily approach to care and has the

**FIG 5** Probability of target attainment for intraperitoneal ceftazidime q48h dosing regimens during day 2 (24 to 48 h).

**FIG 6** Probability of target attainment for intraperitoneal ceftazidime q48h dosing regimens for entire dosing interval (0 to 48 h).
potential for better adherence. Conversely, extending the interval to every-other-day dosing may be preferred to reduce patient manipulations. Given the wide safety window of ceftazidime, our preference is daily dosing to maximize PTA and minimize the likelihood of missed doses.

Our findings highlight the need for reevaluation of the dosing of older antibiotics commonly used in patients on CAPD. Utilizing cost-saving antibiotic regimens is advantageous to dialysis facilities, particularly since the implementation of the End-Stage Renal Disease Prospective Payment System (a.k.a. “the Bundle”) (31). This often means selecting older, generic products in preference to newer brand name drugs. To ensure the continued utility of older agents and maximize their associated outcomes, dosing schemes should be redefined using the approach described here (32). Pharmacokinetic–pharmacodynamic system analyses are commonly employed in the development of new antimicrobial agents to guide the dose selection process, and our findings clearly demonstrate the need to conduct these types of analyses for commonly used antibiotics in PD.

Several things should be considered when interpreting our findings. An important limitation of this study is that noninfected patients were used in the PK analyses. Since infection may facilitate peritoneal transport of antibiotics into the central compartment, our results should be viewed as a conservative estimate of PTA. However, further studies are needed to test this hypothesis. Ryckelynck et al. found no statistical difference in dialysate concentrations of ceftazidime in patients with or without infection (8). However, only a small sample of patients were studied and the findings were subject to type II error. Clearly, more studies on the impact of active infection on the pharmacokinetic and pharmacodynamic profiles are required as we revisist dosing of commonly used antibiotics in PD.

In conclusion, on the basis of our results, we recommend intraperitoneal ceftazidime at 1.5 to 2 g every 24 to 48 h for nonperitoneal infection. While PTA was adequate in the bloodstream, no currently recommended dosing scheme was pharmacodynamically optimal for treatment of peritonitis. To maximize the 60% T > MIC for peritoneal infections caused by pathogens with MICs of ≤8 mg/liter, a 3-g loading dose is needed on day 1, and subsequent dosing may be either 1 to 2 g i.p. q24h or 2 g i.p. q48h. The current clinical practice recommendations should be reevaluated given the findings that several organisms with MIC values within the susceptibility range would not be adequately treated by the suggested ceftazidime dosing scheme of 1 or 1.5 g i.p. q24h. Of course, all findings need to be validated in the clinical arena.

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