Re-evaluation of ceftazidime dosing recommendations in patients on continuous ambulatory peritoneal dialysis

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ABSTRACT

While intraperitoneal (IP) ceftazidime is commonly used in continuous ambulatory peritoneal dialysis (CAPD) related infections, the ability of IP regimens to achieve 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) IP ceftazidime study that included 10 CAPD patients who received IP ceftazidime at 15mg/kg. The probability of target attainment [concentrations maintained above the minimum inhibitory concentration for >60% of the dosing interval (60% T>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 1, 1.5 and 2 g IP Q24-48h were simulated using ADAPT 5. Mean population pharmacokinetic parameters were as follows: Vc=7.57L, Vpd=2.44L, Cl=0.379L/h, k12=4.66h⁻¹, k21=4.88h⁻¹, k13=0.111h⁻¹, k31=0.227h⁻¹. In serum, the probability of target attainment for MICs ≤8 mg/L exceeded 90% for 1.5-2g IP Q24-48h. However, no tested regimen provided adequate dialysate exposure at MICs ≥8 mg/L on day one without use of a 3-gram loading dose (post hoc analysis). On day two, 1.5-2g IP Q24h or 2 g IP Q48h provided adequate exposure in the peritoneal cavity. Results should be validated in the presence of infection. Ceftazidime IP 1.5-2g Q24-48h is recommended for non-peritoneal infections. For peritonitis, a 3-gram load with maintenance dosing of 1-2 g IP Q24h or 2 g IP Q48h is recommended.
INTRODUCTION:

Peritoneal dialysis (PD) is the life-sustaining treatment used by nearly 30,000 Americans with end-stage kidney disease. Infection remains an important complication for the PD population, and significantly contributes to hospitalizations, mortality and dialysis modality failure. All-cause infections account for nearly 600 hospital admissions per 1000 PD patient-years, and risk for infection-related hospitalization is higher amongst patients on PD than for those on hemodialysis. While infection is the second most common cause of death among PD patients, infectious disease processes likely also contribute to cardiovascular events, the most common cause of mortality. Despite the clear need for clinically sound antibiotic dosing recommendations in the PD patient population, literature in this area is often limited or conflicting.

Empiric antibiotic therapy for patients on PD with suspected or documented infections should provide a broad spectrum of coverage for both Gram-positive and -negative organisms. Although aminoglycosides remain important options for Gram-negative coverage, concerns of ototoxicity or loss of residual kidney function exist, and attainment of 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. For these reasons, beta-lactam antibiotics, like ceftazidime, with extensive Gram-negative coverage are preferred. To date, multiple pharmacokinetic (PK) studies of intraperitoneal (IP) ceftazidime have been conducted and have recommended a range of dosing schemes with varying antibiotic dwell times, weight-based versus fixed doses, dosing amounts, continuous versus
intermittent dosing and differing frequencies of administration. On the basis of data from these studies, the current peritoneal dialysis-related infections guideline suggests using 1 to 1.5 g ceftazidime administered via the IP route every 24 hours for the treatment of peritonitis. This recommendation varies from the approved ceftazidime labeling by the Food and Drug Administration (FDA) which recommends 250 mg in 2L of peritoneal dialysate for IP administration.6

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

METHODS:
Study Design and Population: Data were obtained from a previously conducted prospective, single dose PK study to conduct this analysis. The study included adult (≥ 18 years), non-infected patients on a stable continuous ambulatory PD (CAPD) regimen for at least two months. Patients were excluded if they had peritonitis or received antibiotics within the...
previous 4 weeks, had allergy to cephalosporin drugs or had a documented anaphylactic reaction to beta-lactam medications. Ten patients (4 women and 6 men) were studied, four of whom had anuria. The mean clinical characteristics were as follows: age 48.2±14.2 years, weight 91.3±21.4 kg, body mass index 30.8±6.9 kg/m², and dialysis vintage 25.3±18.6 months. The mean ceftazidime dose administered was 1378.5±316 mg.

**Study Procedure:** Eligible patients received a standardized CAPD prescription of four 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. Daily dwells were 6 hours, 4 hours, 6 hours and 8 hours, respectively. Ceftazidime 15 mg/kg was added to a 2-liter dialysate bag and administered during the first daily dwell for 6 hours in duration. Blood and dialysate samples collected at 0.5, 1, 2, 3, 6 and 24 hours 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 Non-Parametric 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 IP administration of ceftazidime:

\[
\frac{dX_1}{dt} = -\left(\frac{CL}{V} + k_{12} + k_{13}R_2 + k_{13}R_3\right)X_1 + k_{21}X_2 + k_{31}X_3R_2 + k_{31}X_4R_3 + k_{31}X_5R_4 + k_{31}X_6R_5
\]
\[
\frac{dX_2}{dt} = k_{12}X_1 - k_{21}X_2
\]

\[
\frac{dX_3}{dt} = R_1 + k_{13}X_1R_2 - k_{31}X_3R_2
\]

\[
\frac{dX_4}{dt} = k_{13}X_1R_3 - k_{31}X_4R_3
\]

\[
\frac{dX_5}{dt} = k_{13}X_1R_4 - k_{31}X_5R_4
\]

\[
\frac{dX_6}{dt} = k_{13}X_1R_5 - k_{31}X_6R_5
\]

where \(X_1\): amount of ceftazidime in the central compartment; \(X_2\): amount of ceftazidime in the peripheral compartment; \(X_3\): amount of ceftazidime in the peritoneal cavity during the first PD dwell; \(X_4\): amount of ceftazidime in the peritoneal cavity during the second dwell; \(X_5\): amount of ceftazidime in the peritoneal cavity during the third dwell; \(X_6\): amount of ceftazidime in the peritoneal cavity during the fourth dwell; \(CL\): non-dialytic clearance from central compartment (liters per hour); \(V\): apparent volume of the central compartment (liters); \(k_{12}\) and \(k_{21}\): first-order intercompartmental transfer rate constants between central and peripheral compartments (hours\(^{-1}\)); \(k_{13}\) and \(k_{31}\): first-order intercompartmental transfer rate constants between central and peritoneal compartments (hours\(^{-1}\)); \(R_1\): time-delimited zero-order input rate for ceftazidime (piece-wise input function) into the peritoneal cavity (mg per hour); \(R_2 - R_5\): 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 total observation variance was proportional to 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. Gamma is an overall measure of all the other sources of intra-individual variability besides the assay error. In this way, one can calculate how much of the total standard deviation is due to the assay standard deviation, and how much is due to the remaining overall environmental standard deviation.\textsuperscript{22, 23}

Upon convergence, Bayesian estimates for each patient were obtained using the “population of one” utility in BigNPAG.\textsuperscript{19} For each model, the mean, median and modal values were employed as central tendency measures for estimates of population parameters, and were evaluated in the maximum a posteriori (MAP) Bayesian analysis. Scatter plots were evaluated for individual patients and for the population. Goodness-of-fit was assessed by regression with an observed versus predicted plot, coefficients of determination and log-likelihood values. Predictive performance was evaluated using mean weighted error (measure of bias) and the bias-adjusted mean weighted squared error (measure of precision). Due to limited sample size and number of samples per patient, the magnitude of $\phi$-shrinkage was calculated based on the method of Savic and Karlsson for clearance and each volume term.\textsuperscript{24}

Monte Carlo simulation: The mean parameter vector and major diagonal covariance matrix from the population PK model were embedded in Subroutine PRIOR of the ADAPT 5 program package.\textsuperscript{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 gram IP every 24 hours, 1 gram IP every 48 hours, 1.5 grams IP every 24 hours, 1.5 grams IP every 48 hours, 2 grams IP every 24 hours and 2 grams IP every 48 hours.

Normal and log-normal distributions were considered for each parameter in the final PK model used in the simulations. The selected distributions of the PK parameters used in the simulations was based on ability of the normal vs. 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 in the peritoneal cavity. Protein binding was assumed to be 10% in the serum. Ceftazidime found in the peritoneal cavity was assumed to be free drug, since extent of protein binding in this compartment is unknown.

The pharmacodynamic target selected for analyses was free ceftazidime concentration above the MIC for at least 60% of the dosing interval (60% T>MIC). 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 MIC values 0.25 mg/L to 16 mg/L in the: 1) serum (central compartment), and 2) peritoneal cavity. Per the Clinical and Laboratory Standards Institute (CLSI) breakpoints, Enterobacteriaceae are considered susceptible to ceftazidime at MIC values ≤4 mg/L, and at ≤ 8 mg/L for non-lactose fermenting Gram-negative rods, such as Pseudomonas aeruginosa. Three windows of time were evaluated for PTA: 0-24 hours (i.e. Day 1), 24-48 hours (i.e. Day 2), etc.
and 0-48 hours (for Q48 hour regimens only). For every other day dosing schemes, it is unknown over which interval is most appropriate to conduct PTA analyses (i.e. to examine PTA during each daily 24-hour interval, or to examine PTA over the entire 48-hour dosing interval). For this reason, PTA analyses were conducted for partitioned daily time intervals (i.e. 0-24 hours and 24-48 hours), as well as over the entire dosing interval (0-48 hours). For treatment of peritonitis, regimens were considered acceptable if they achieved at least 90% PTA at susceptible MICs in both the central compartment and in the peritoneal cavity. Regimens were considered acceptable for non-peritoneal infection if they achieved at least 90% PTA at susceptible MICs in the central compartment.

Monte Carlo Simulation was also used to evaluate the predictive performance of the population pharmacokinetic model. Please note that a variety of doses were administrated across the patients as the original study was dosed on a 15 mg/kg basis. Since the patients received different doses, we simulated the average dose (1400 mg) received during the original PK study in the study in plasma and peritoneal cavity using the mean parameter vector values, then dispersed the patients’ data points around the simulated points. The fidelity by 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. Mean weighted error, a measure of bias, for observed versus predicted ceftazidime concentrations was -0.04, -0.17 and 0.041 mg/L for plasma, peritoneal cavity (first dwell) and peritoneal cavity (fourth dwell), respectively. Precision, measured using bias-adjusted mean weighted squared error, was 0.47,
1.85 and 0.018 mg/L for plasma, peritoneal cavity (first dwell) and peritoneal cavity (fourth dwell) concentrations, respectively. The observed vs. 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 (Figure 1). The coefficients of determination ($r^2$) were $\geq 0.94$ for all outputs and the measures of bias and precision were acceptable. Population PK model parameter estimates for ceftazidime are provided in Table 1. The $\hat{\phi}$-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. Simulated plasma and peritoneal cavity concentrations for 1400 mg IP ceftazidime is shown in Figure 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, ceftazidime concentrations at the midpoint and end of dosing interval were well captured around the central tendency.

Probability of Pharmacodynamic Target Attainment (PTA) Analyses: Figure 3 shows the PTA for each regimen in both the peritoneal and central compartments during the first day (from 0-24 hours) following IP dose administration. In the peritoneal cavity, no regimen provided adequate drug exposure during the first 24 hours for organisms with MIC $> 4$mg/L. In the central compartment, 1.5g and 2g doses, but not 1g, provided adequate coverage for all susceptible organisms (MIC$\leq 8$ mg/L) during day 1. No regimen was acceptable at MIC of 16 mg/L, which is outside the CLSI susceptible range of the drug.
On day 2, a second dose was simulated for the tested regimens of 1g Q24h, 1.5g Q24h and 2g Q24h. Results of the PTA analyses for each of these regimens during the second treatment day (24-48 hours) are depicted in Figure 4. During day 2, 1.5 and 2g Q24h provided acceptable drug exposure in the peritoneal cavity at susceptible MICs ≤ 8 mg/L. All Q24h regimens (i.e. 1-2 g Q24h) yielded PTA > 90% for non-peritoneal infections across the range of MICs evaluated.

PTA analyses for every other day dosing schemes (i.e. 1g Q48h, 1.5g Q48h and 2g Q48h) are depicted in Figures 5 and 6. Figure 5 shows the PTA analyses for the second day (24-48 hours) for each Q48h regimen. On day 2, only 2g Q48h was highly likely to achieve the pharmacodynamic target in the peritoneal cavity over the range of MICs up to 8 mg/L. For non-peritoneal infections, 1-2g Q48h provided adequate drug exposure in the central compartment for MICs of 8 mg/L or less during the second day. The PTA analysis for every other day dosing regimens over the entire two-day dosing interval (from 0-48 hours) is shown in Figure 6. No regimen provided adequate concentrations for peritonitis at 8 mg/L MIC. However, non-peritoneal infection was adequately covered by 1.5-2g Q48h at MICs up to 8 mg/L.

DISCUSSION:

Our understanding of ceftazidime’s exposure-response relationships has advanced considerably since its FDA approval in 1985. This, combined with evolving susceptibility patterns among key Gram-negative pathogens, highlight 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.\textsuperscript{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 antibiotic regimens.

There are several important considerations when evaluating the appropriateness of an antibiotic dosing scheme for patients on PD. First, inter-patient 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.

Cognizant of these issues, we used population PK modeling and Monte Carlo simulation to evaluate IP 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 1.5-2 grams of ceftazidime IP every 24 to 48 hours was appropriate for treatment of non-peritoneal infections in the central compartment. These
Regimens were associated with a greater than 90% probability of achieving 60% \( T>MIC \) for MIC values up to 8 mg/L in the serum. This range of MIC values represents the susceptible range for many Gram-negative infections, including Enterobacteriaceae and Pseudomonas.

Findings in the peritoneal cavity were not as straightforward. Despite intraperitoneal administration, drug distribution from the peritoneal cavity into the central and peripheral compartments results in lower drug exposures in the peritoneal cavity, particularly on the first day of therapy. As such, no regimen provided adequate exposure at an MIC of 8 mg/L during the first 24 hours. Given the importance of early, appropriate therapy, this finding has important implications for clinical practice. Current clinical practice guidelines recommend providing empiric therapy that includes coverage for \textit{Pseudomonas aeruginosa} when peritonitis is suspected. Since the CLSI susceptibility breakpoint for non-lactose fermenting Gram-negative bacteria like \textit{Pseudomonas aeruginosa} is 8 mg/L, ceftazidime doses of 1-2 grams IP cannot be recommended for peritoneal infections. In a post-hoc analysis (data not shown), we found that a 3g IP loading dose of ceftazidime was required to achieve >90% probability of achieving 60% \( T>MIC \) in peritoneal cavity at an MIC of 8 mg/L during the first 24 hours. Following this loading dose, 1g Q24h provided adequate exposure in the peritoneal cavity during day 2. Therefore, subsequent to a 3g IP loading dose, 1-2 gram IP Q24 hours or 2 grams Q48 hours 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 grams daily) in patients with kidney disease. Therefore patients receiving a loading dose should be closely monitored for neurologic complications, principally confusion and myoclonus. The decision to use daily or every other day dosing should be
driven by clinician and patient preferences, and severity of infection. Daily IP dosing offers a consistent daily approach to care and has the 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 re-evaluation 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”). 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. Pharmacokinetic-pharmacodynamic systems 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 non-infected 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. 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 revisit dosing of commonly used antibiotics in PD.

In conclusion, on the basis of our results, we recommend intraperitoneal ceftazidime 1.5-2g every 24-48 hours for non-peritoneal infection. While PTA was adequate in bloodstream, no currently recommended dosing scheme was pharmacodynamically optimal for treatment of peritonitis. To maximize 60% T>MIC for peritoneal infections with MIC values ≤ 8 mg/L, a 3 gram loading dose is needed on day 1, and subsequent dosing may be either 1-2 g IP Q24h or 2 g IP Q48. Current clinical practice recommendations should be reevaluated given the findings that several organisms within the susceptible range would not be adequately treated by the suggested ceftazidime dosing scheme of 1-1.5 grams IP every 24 hours. Of course, all findings need to be validated in clinical arena.

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REFERENCES:


Table 1. Population pharmacokinetic parameter estimates.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_c )</td>
<td>7.57 ± 3.58 L</td>
</tr>
<tr>
<td>( CL )</td>
<td>0.379 ± 0.198 L/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 L</td>
</tr>
</tbody>
</table>

\( V_c \): Apparent volume of the central compartment; \( CL \): non-dialytic clearance from the central compartment; \( k_{12}, k_{21} \): intercompartmental transfer rate constants (first order) between the central and peripheral compartments; \( k_{13}, k_{31} \): intercompartmental transfer rate constants (first order) between the central and peritoneal compartments; \( V_{pd} \): Apparent volume of the peritoneal cavity.
FIGURE LEGENDS:

Figure X. Observed versus predicted plots for plasma concentrations (Panel A) and peritoneal cavity concentrations during dwell 1 (Panel B) and dwell 4 (Panel C).

Figure 2. Plasma (Panel A) and peritoneal (Panel B) ceftazidime concentration versus time profiles.

Figure 3. Probability of target attainment for intraperitoneal ceftazidime dosing regimens during day 1 (0-24 hours).

Figure 4. Probability of target attainment for intraperitoneal ceftazidime Q24 hour dosing regimens during day 2 (24-48 hours).

Figure 5. Probability of target attainment for intraperitoneal ceftazidime Q48 hour dosing regimens during day 2 (24-48 hours).

Figure 6. Probability of target attainment for intraperitoneal ceftazidime Q48 hour dosing regimens for entire dosing interval (0-48 hours).