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Identification of Optimal Renal Dosage Adjustments for Traditional and Extended-Infusion Piperacillin-Tazobactam Dosing Regimens in Hospitalized Patients▽

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This study examined the effect of various levels of renal impairment on the probability of achieving free drug concentrations that exceed the MIC for 50% of the dosing interval (50% *f*T > MIC) for traditional and extended-infusion piperacillin-tazobactam (TZP) dosing strategies. It also identified optimal renal dosage adjustments for traditional and extended-infusion dosing schemes that yielded probability of target attainment (PTA) and exposure profiles that were isometric to those of the parent regimens. Data from 105 patients were analyzed using the population pharmacokinetic modeling program BigNPAG. To assess the effect of creatinine clearance (CL_{CR}) on overall clearance, TZP clearance was made proportional to the estimated CL_{CR}. A Monte Carlo simulation (9,999 subjects) was performed for the traditional dosing scheme (4.5 g infused during 30 min every 6 h) and the extended-infusion TZP dosing scheme (3.375 g infused during 4 h every 8 h). The fraction of simulated subjects who achieved 50% *f*T > MIC was calculated for the range of piperacillin MICs from 0.25 to 32 mg/liter and stratified by CL_{CR}. The traditional TZP regimen displayed the greatest variability in PTA across MIC values, especially for MIC values exceeding 4 mg/liter, when stratified by CL_{CR}. In contrast, the PTA for the extended-infusion TZP regimen exceeded ≥80% for MIC values of ≤8 mg/liter across all CL_{CR} strata. All regimens were associated with suboptimal PTA for MIC values of ≥32 mg/liter irrespective of the CL_{CR}. The CL_{CR} adjustments for traditional and extended-infusion TZP dosing regimens should be considered at a CL_{CR} of ≤20 ml/min.

Piperacillin-tazobactam (TZP), a combination product of a semisynthetic penicillin and a beta-lactamase inhibitor, exhibits broad-spectrum activity and low toxicity, and it is indicated for a variety of clinical infections (1). TZP is excreted primarily from the body via the kidney, with the majority (~70%) being eliminated as unchanged drug in the urine (1). Because TZP is eliminated primarily by the kidneys, dose alterations are required for patients with renal impairment.

Despite 15 years of clinical experience, the effect of renal impairment on the pharmacodynamic profile of TZP has not been well evaluated. It is well known that beta-lactam drugs such as TZP exert bactericidal activity in a time-dependent manner, with the time the free drug concentrations exceed the MIC during the dosing interval (*f*T > MIC) being the key pharmacodynamic parameter (4, 6, 7, 11, 12, 22, 27, 29). For beta-lactams like TZP, it appears that bactericidal activity is optimized when *f*T > MIC exceeds 50% of the dosing interval (designated 50% *f*T > MIC) (8, 10). Among the studies that have characterized the ability of various TZP dosing strategies to achieve 50% *f*T > MIC (13, 17, 24), all have reported the overall probability of target attainment (PTA); we are unaware of any previous study that stratified PTA by renal function. Additionally, no study has assessed the effect of renal dose adjustments on the ability to achieve the desired pharmacodynamic target. An understanding of the effects of renal impairment and renal dose adjustment schemes on the pharmacodynamic profile are clinically important, because the majority of patients receiving TZP have some degree of renal impairment and often are administered a TZP regimen that is adjusted accordingly. While effectiveness is often the primary interest, minimizing TZP accumulation or excessive exposure also is of great importance. In the presence of renal dysfunction, TZP accumulation may occur and result in unnecessary toxicity. Quantifying the degree of TZP accumulation that results from diminished renal function will assist in identifying the creatinine clearance (CL_{CR}) breakpoint and dose adjustment that would leave the PTA substantially unaltered and still not result in profound accumulation.

This study had two specific aims. First, we examined the effect of various levels of renal impairment on the probability of achieving 50% *f*T > MIC for traditional and extended-infusion TZP dosing strategies. Second, we sought to identify renal dosage adjustments for traditional and extended-infusion dosing schemes that yielded PTA and exposure profiles for the TZP renal dosing strategies that were isometric to parent regimens. For the purpose of the analysis, we characterized only the pharmacodynamic profile of piperacillin. We did not examine the pharmacodynamic profile of tazobactam, because current doses of tazobactam in the TZP formulation have been shown to be sufficient for an antibacterial effect when the target is attaining a free-drug concentration exceeding the MIC for 50% of the dosing interval (26).

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MATERIALS AND METHODS

Patient population. Pharmacokinetic (PK) data from 105 hospitalized patients (963 samples in total) were obtained from two sources. First, plasma concentration-time data were obtained from four open-label studies evaluating the pharmacokinetics of TZP (two single-dose studies and two multiple-dose studies). These studies included hospitalized patients with clinical indications for TZP therapy (19). Among the 139 patients from these studies, complete PK data with creatinine clearance (CL_{CR}) information were available for 93 patients (873 plasma drug concentrations). The CL_{CR} values for all subjects were estimated by the Cockcroft-Gault method (5).

The second source of pharmacokinetic data was obtained from 12 patients enrolled in a prospective PK study that was conducted at the Albany Medical Center Hospital, a 651-bed teaching hospital in Albany, NY. This study included patients hospitalized for >48 h and receiving 3.375 g TZP intravenously (i.v.) every 8 h during a 4-h infusion period. In total, 90 plasma drug samples were assessed for these 12 patients (20). All samples for both sets of PK data were analyzed using high-pressure liquid chromatography (HPLC) (14, 15).

Population pharmacokinetic modeling methods for hospitalized patients. All data were analyzed in a population pharmacokinetic model using the Big Non-Parametric Adaptive Grid with adaptive γ (BigNPAG) program of Leary et al. (18). The pharmacokinetic model was parameterized as a standard two-compartment model with zero-order infusion. Elimination from the central compartment and all intercompartmental distribution processes were modeled as first-order processes. To assess the impact of renal function on overall clearance, piperacillin clearance was made proportional to the estimated CL_{CR} as follows: (CL_{slope} × estimated CL_{CR}) + CL_{int}), where CL_{slope} is the clearance slope and CL_{int} is the clearance intercept.

The inverse of the estimated assay variance was used as the first estimate for weighting in the PK model. Weighting assumed that total observation variance was proportional to assay variance, which was determined on a between-day basis. The analysis was performed with adaptive γ, a scalar that multiplies the polynomial described above and that is optimized with each cycle to produce the best approximation to the homoscedastic assumption. Adaptive γ was fixed at one for the analysis.

Upon attaining convergence, Bayesian estimates for each patient were obtained by using the population-of-one utility in the BigNPAG program. The mean and median values were used as measures of the central tendency of the population parameter estimates and were evaluated in the Bayesian analysis. Scatter plots were examined for individual patients and for the population as a whole. Goodness of fit was assessed by regression with an observed-predicted plot, coefficients of determination, and log-likelihood values. Predictive performance evaluation was based on weighted mean errors and the bias-adjusted weighted mean squared errors.

Model validation. As an additional evaluation of the predictive performance of the PK model, a validation PK model was developed to assess the validity of the clearance estimate. We assessed the validity of the clearance estimate because clearance is the major determinant of fT > MIC in the model. For the validation model, 80% of subjects included in the overall model were randomly selected, and their TZP serum concentration data were modeled using BigNPAG as described above. This validation model was used to predict the TZP clearance for the remaining 20% of subjects withheld from the validation model. The overall clearance for each of the remaining subjects was predicted using the median parameter estimates for CL_{INT} and CL_{slope} and their individual CL_{CR} values (clearance = CL_{slope} × estimated CL_{CR} + CL_{INT}). These clearance estimates served as the predicted clearance estimates and were compared to the median observed maximum *a posteriori* (MAP) Bayesian estimate of clearance for each patient in the overall model. Goodness of fit was assessed by regression with an observed-predicted plot, and predictive performance evaluation was based on bias and precision. Bias was calculated as the mean percent error: [(observed clearance − predicted clearance)/observed clearance]. Precision was calculated as the mean percent squared error: [(observed clearance − predicted clearance)^2/observed clearance].

MCS. (i) Probability of target attainment stratified by renal function. Because of its predictive performance in the Bayesian goodness-of-fit assessment, the median parameter vector and covariance matrix from the population PK models were embedded in the PRIOR subroutine of the ADAPT II package of the programs of D'Argenio and Schumitzky (ADAPT II User's Guide, Pharmacokinetics/Pharmacodynamics System Analysis Software; Biomedical Simulations Resource, Los Angeles, CA) (9). The population simulation without the process noise option was used. A 9,999-subject Monte Carlo simulation (MCS) was performed using the median parameter estimates and covariance matrix for the nosocomial pneumonia FDA-approved dosing scheme (4.5 g infused during 30 min every 6 h) and the extended-infusion TZP dosing scheme used at the Albany Medical Center (3.375 g infused during 4 h every 8 h). Since the primary aim of the study was to examine the PTA across various levels of renal function, the estimated CL_{CR} was fixed at values of 20, 40, 60, 80, 100, and 120 ml/min.

TABLE 1. Demographic features of modeled subjects receiving TZP[a]

Demographic	Result
Age (yr)	53.2 (16.4)
Sex (male)	63.0 (60.0)
Height (m)	1.7 (0.12)
Weight (kg)	71.3 (13.7)
CL_{CR} (ml/min)	91.6 (33.6)
Body surface area (m^2)	1.8 (0.22)

[a] All values are presented as the number of subjects (percentage) or mean value (standard deviation), unless otherwise indicated.

Concentration-time profiles for each of these dosing regimens were simulated for 24 h, and these data were used for the PTA analyses. Since early appropriate therapy has been identified as a major determinant of outcomes in patients with serious infections (16), we believe it is more important to simulate at concentration-time profiles at hour 24 rather than at true steady state. The piperacillin PK data were adjusted for 30% protein binding to reflect unbound drug concentrations in the data analysis, and free drug was used for all calculations. For each regimen, the fraction of simulated subjects who achieved 50% *f*T > MIC was calculated for the range of piperacillin MICs (in the presence of tazobactam) from 0.25 to 32 mg/liter and was stratified by CL_{CR}. Both normal and log-normal distributions were evaluated. These were discriminated on the ability to recreate the original median parameter values and corresponding standard deviations from the population analysis. Systat for Windows (version 10.2) was used for all data transformations, and STATA version 9.2 (College Station, TX) was used for graphing functions.

(ii) Renal dosage adjustments. For our second aim, we determined the optimal renal dosage adjustments for traditional TZP dosing (TZP 4.5 g i.v. every 6 h as a 30-min infusion) and extended-infusion TZP dosing (TZP 3.375 g i.v. every 8 h as a 4-h infusion). For traditional TZP dosing, a 9,999 MCS (ADAPT II) was performed for the current FDA-approved renal dose adjustment regimen for TZP 4.5 g every 6 h as a 30-min infusion (3.375 g TZP every 6 h [30 min infusion] at a CL_{CR} of 40 ml/min) (1). We also evaluated 3.375 g TZP every 6 h (30 min infusion) at a CL_{CR} of 20 ml/min as an alternative renal dose adjustment scheme. For extended-infusion TZP dosing with a base regimen of 3.375 g every 8 h as a 4-h infusion, a 9,999 MCS (ADAPT II) was performed for the following renal dose adjustment regimens: 3.375 g i.v. every 12 h (4-h infusion) at a CL_{CR} of 40 ml/min and 3.375 g i.v. every 12 h (4-h infusion) at a CL_{CR} of 20 ml/min.

For each of these renal dose adjustment regimens, the Monte Carlo simulation data were used to determine the probability of achieving 50% *f*T > MIC for MICs from 0.25 to 32 mg/liter at the candidate renal dose adjustment CL_{CR} thresholds. The PTA (50% *f*T > MIC) were examined at the candidate CL_{CR} dose adjustment thresholds, because these CL_{CR} levels provide the most conservative estimates of PTA for each of the potential renal dose adjustment regimens. To determine the degree of TZP accumulation, we calculated the ratio of the distribution of the area under the concentration-time curves at steady state (AUC_{24SS}) of the parent regimen at the CL_{CR} threshold where renal dosage adjustment would occur (e.g., $CL_{CR} \leq 40$ ml/min or $CL_{CR} \leq 20$ ml/min) relative to the AUC_{24SS} of the parent regimen at a CL_{CR} of 100 ml/min. We examined the AUC_{24SS} of the parent regimen at the CL_{CR} dose adjustment threshold, because this is the point of maximal exposure for a given TZP renal dosing scheme. Similarly to the stratified renal function PTA analyses, concentration-time profiles for each of these dosing regimens were simulated for 24 h.

RESULTS

Demographic features of the 105 patients who provided plasma samples are displayed in Table 1. Among the 105 patients, 63 (60%) were male. The mean (standard deviations) age of the patients was 53.2 (16.4) years. The mean (standard deviation) CL_{CR} of the population was 91.6 (33.6) ml/min. Only three patients had CL_{CR} values of less than 40 ml/min.

TABLE 2. Evaluation of the predictive performance of piperacillin population models[a]

Model	V_1	CL_{int}	CL_{slope}	K_{cp}	K_{pc}
Overall					
Mean	13.32	3.76	0.102	2.02	4.47
Median	12.40	3.35	0.098	0.62	1.33
Standard deviation	5.72	2.66	0.057	3.07	6.37
Validation					
Mean	13.37	3.57	0.107	3.57	6.25
Median	10.27	3.16	0.098	1.25	1.82
Standard deviation	6.12	2.74	0.060	4.91	7.24

[a] K_{cp}, transfer rate constant from the central compartment to the peripheral compartment (per hour). K_{pc}, transfer rate constant from the peripheral compartment to the central compartment (per hour). V_1, volume of the central compartment (liters). CL_{slope}, fraction of piperacillin clearance due to creatinine clearance (liters per hour). CL_{int}, clearance due to non-renal means (liters per hour).

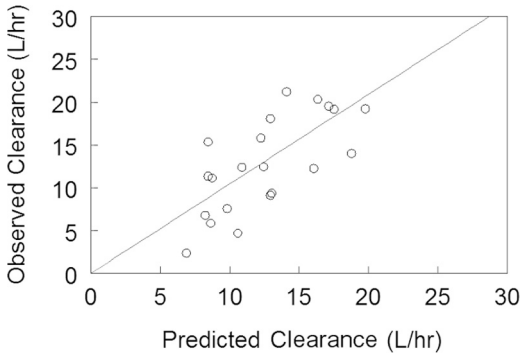


FIG. 1. Plot of the predicted median clearance estimates from the validation model versus the observed MAP Bayesian estimate of clearance from the overall model for the 21 patients withheld from the validation model.

Population pharmacokinetic analysis. (i) Overall model. The mean and median population parameter estimates and associated dispersions identified by BigNPAG are provided in Table 2. Prior to the Bayesian analysis, the median and mean best-fit regression lines were 0.87 × predicted + 6.7 and 1.0 × predicted + 3.3, respectively. The R^2 values for the median and mean were 0.78 and 0.77, respectively. The predictive performance measures of the mean and median estimates of central tendencies for the population model after the Bayesian step are displayed in Table 3. The model fit was highly acceptable for both the mean and the median. Because of the slightly higher R^2, lower bias-adjusted mean weighted square error, and smaller intercept term in the observed-predicted plot, the median parameter estimates were selected for the Monte Carlo simulation analyses.

(ii) Validation model. The mean and median population parameter estimates and associated dispersions identified by BigNPAG are provided in Table 2, and the predictive performance measures of the mean and median estimates of central tendencies for the validation model after the Bayesian step are displayed in Table 3. The parameter estimates and predictive performance of the validation model were highly consistent with the overall PK model. The clearance observed versus predicted plot for the 20% of patients withheld from the validation model are displayed in Fig. 1. Overall, the observed versus predicted plot was highly acceptable, and its predicted performance is consistent with a previously published population PK model validation (23). The best-fit regression line was observed = 1.014 × predicted + 0.032, and the R^2 was 0.493. The mean bias was −0.16, and the mean precision was 1.64.

TABLE 3. Goodness of fit and predictive performances of TZP population models (serum)

Model	Mean	Median
Overall		
Regression line observed[a]	−1.382 + 1.1072 × predicted	0.143 + 1.070 × predicted
R^{2b}	0.9487	0.9517
Mean weighted error, in mg/liter	0.0199	−0.2011
Bias-adjusted mean weighted square error, in $(mg/liter)^2$	1.837	1.181
Validation		
Regression line observed[a]	−1.997 + 1.1321 × predicted	−0.777 + 1.087 × predicted
R^{2b}	0.94	0.94
Mean weighted error, in mg/liter	−0.0830	−0.1687
Bias-adjusted mean weighted square error, in $(mg/liter)^2$	1.146	1.187

[a] The observed versus predicted plot regression line is the best-fit regression line for the observed-predicted plot after the Bayesian step.
[b] R^2 is the coefficient of determination for the best-fit linear regression for the predicted-observed plot after the Bayesian step.

(iii) Monte Carlo simulation of hospitalized patients stratified by renal function. The results of PTA analyses stratified by CL_{CR} are displayed in Table 4. The FDA-approved regimen (4.5 g i.v. every 6 h via 30-min infusion) displayed the greatest variability in PTA across MICs. The PTA was ≥80% for MICs of ≤2 mg/liter in the intermittent infusion regimens at all levels of CL_{CR}. However, the PTA fluctuated considerably for MICs exceeding 4 mg/liter when stratified by CL_{CR}. In contrast, the PTA for the extended-infusion TZP regimen exceeded ≥95% for MICs of ≤8 mg/liter. Both TZP regimens were associated with suboptimal PTA for MICs of ≥32 mg/liter, irrespective of the CL_{CR}.

Renal dosage adjustment analysis. (i) FDA nosocomial pneumonia regimen (4.5 g TZP i.v. every 6 h as a 30-min infusion). The results of the PTA analyses for the renal dose adjustment regimens are displayed in Table 5. At a CL_{CR} of 100 ml/min, the PTA for 4.5 g TZP every 6 h (30-min infusion) sharply decreased (<80%) after MICs exceeded 4 mg/liter for 4.5 g every 6 h via 30-min infusion. The dosage adjustment of the parent regimen to 3.375 g every 6 h as a 30-min infusion at CL_{CR} of 40 and 20 ml/min both resulted in an increased PTA relative to that of the parent regimen among patients with a CL_{CR} of 100 ml/min. The candidate renal dose adjustment regimens had similar PTA for MICs of ≤8 mg/liter, but higher PTA were noted for the candidate regimen renal dose adjusted at a CL_{CR} of 20 ml/min for MICs of ≥16 mg/liter (Table 5).

Figure 2A shows the distribution of exposure ratios (AUC_{24SS} fixed at a CL_{CR} of 40 ml/min relative to the AUC_{24SS} distribution fixed at a CL_{CR} of 100 ml/min) and

TABLE 4. PTA of various TZP dosing regimens stratified by CL_{CR} and MIC[a]

CL_{CR} (ml/min)	Traditional regimen at TZP MIC (mg/liter):								Extended-infusion regimen at TZP MIC (mg/liter):							
	0.25	0.5	1	2	4	8	16	32	0.25	0.5	1	2	4	8	16	32
120	0.96	0.94	0.90	0.83	0.73	0.57	0.36	0.13	0.99	0.99	0.99	0.99	0.99	0.96	0.62	0.11
100	0.98	0.96	0.93	0.88	0.81	0.67	0.46	0.19	0.99	0.99	0.99	0.99	0.99	0.97	0.73	0.17
80	0.99	0.98	0.96	0.93	0.87	0.77	0.58	0.30	0.99	0.99	0.99	0.99	0.99	0.98	0.82	0.27
60	0.99	0.99	0.98	0.96	0.92	0.84	0.70	0.43	0.99	0.99	0.99	0.99	0.99	0.99	0.90	0.43
40	0.99	0.99	0.99	0.98	0.96	0.92	0.84	0.64	0.99	0.99	0.99	0.99	0.99	0.99	0.95	0.62
20	0.99	0.99	0.99	0.99	0.98	0.96	0.91	0.80	0.99	0.99	0.99	0.99	0.99	0.99	0.97	0.81

[a] Traditional regimen, 4.5 g i.v. every 6 h, 30-min infusion; extended-infusion regimen, 3.375 g i.v. every 8 h, 4-h infusion.

demonstrates that all subjects had an exposure ratio of less than a factor of 3. In contrast, waiting to adjust the dose until the CL_{CR} attained 20 ml/min resulted in some subjects experiencing an exposure ratio of greater than 4, although the majority of subjects had an exposure ratio of less than 3 (Fig. 2B).

(ii) Extended-infusion regimen (3.375 g TZP i.v. every 8 h as a 4-h infusion). The results of target attainment analyses for the Monte Carlo simulations are displayed in Table 5. The PTA exceeded 90% for a TZP regimen of 3.375 g i.v. every 8 h as a 4-h infusion at a CL_{CR} of 100 ml/min for MICs of <16 mg/liter. When the interval was lengthened from every 8 h to every 12 h at a CL_{CR} of 40 ml/min, a substantial reduction in PTA was observed for MICs of ≥ 8 mg/liter. In contrast, the PTA profile for 3.375 g i.v. every 12 h at a CL_{CR} of 20 ml/min was identical to the PTA profile for 3.375 g i.v. every 8 h as a 4-h infusion at a CL_{CR} of 100 ml/min.

Figure 2C shows the distribution of exposure ratios (AUC_{24SS} fixed at a CL_{CR} of 40 ml/min relative to the AUC_{24SS} distribution fixed at a CL_{CR} of 100 ml/min) and demonstrates that all subjects had an exposure ratio of less than a factor of 3. In contrast, waiting to adjust the dose until the CL_{CR} attained 20 ml/min resulted in some subjects experiencing an exposure ratio of greater than 4, although the majority of subjects had an exposure ratio of less than 3 (Fig. 2D).

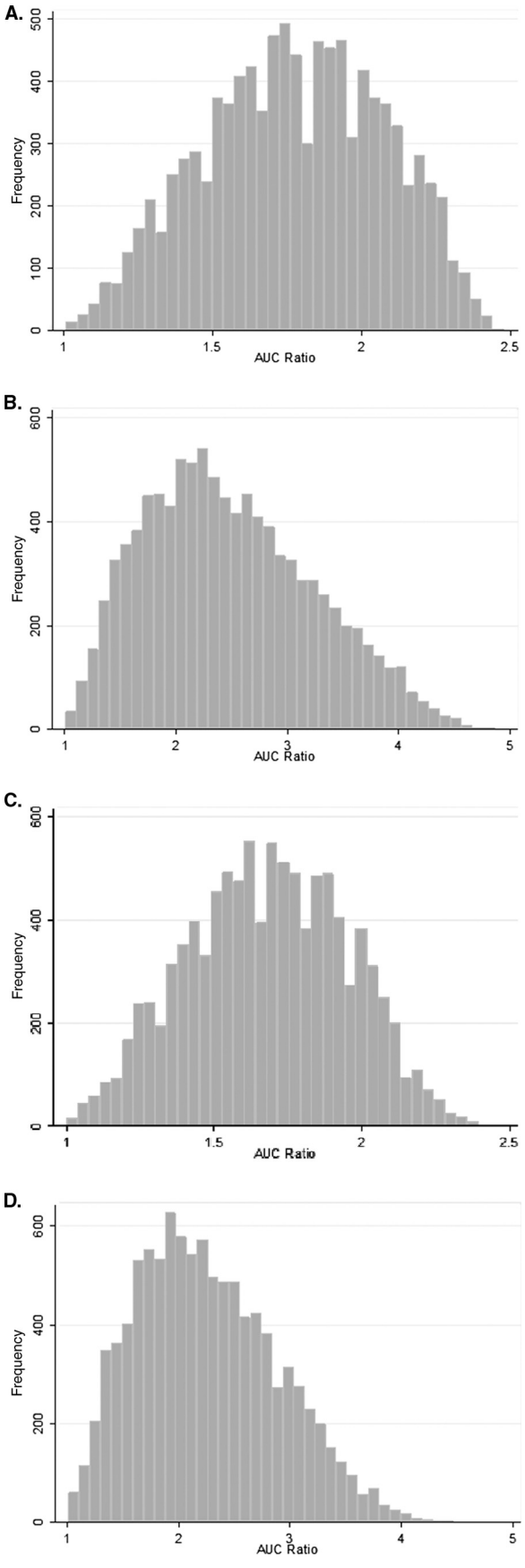
DISCUSSION

Historically, most pharmacodynamic profiling studies have examined the overall PTA without regard to a patient's renal function. It is well known that the majority of beta-lactam antibiotics are eliminated primarily by the kidneys (3). One would anticipate that the PTA varies as a function of the estimated CL_{CR}. The purpose of our analysis was to evaluate the effect of various CL_{CR} estimates on the observed PTA for the FDA-approved TZP nosocomial pneumonia dosing regimen (4.5 g TZP i.v. as a 30-min infusion every 6 h), as well as the extended-infusion TZP dosing strategy (3.375 g TZP i.v. as a 4-h infusion every 8 h) adopted into practice at the Albany Medical Center Hospital. To the best of our knowledge, our analysis is the first to examine the effect of various levels of renal function on the PTA for traditional and extended-infusion TZP dosing strategies among hospitalized patients.

An inverse relationship was observed between PTA and CL_{CR} for both regimens. The extended-infusion TZP regimen was pharmacodynamically superior to the intermittent-infusion TZP regimen. This finding is consistent with previous evaluations (13, 19). Both TZP regimens were associated with suboptimal PTA for MICs of ≥ 32 mg/liter irrespective of the CL_{CR}. These findings may partially explain the results observed in the recent study by Tam et al., which examined 30-day mortality rates among patients with *Pseudomonas aeruginosa* bloodstream infections stratified by the TZP MIC (28). In this study, patients with a *P. aeruginosa* bloodstream infection for which the TZP MIC was 32 or 64 mg/liter who were empirically treated with intermittent-infusion TZP had a 30-day mortality rate in excess of 80%. In contrast, 30-day mortality was 33% if the TZP MIC for the *P. aeruginosa* bloodstream isolate was ≤ 16 mg/liter when empirically treated with intermittent-infusion TZP. Interestingly, treating patients with an alternative (non-TZP) anti-pseudomonal beta-lactam antibiotic for *P. aeruginosa* bloodstream infections with a TZP MIC of 32 or 64 mg/liter resulted in a 30-day mortality of 22%. These results and data from previous TZP PTA analyses (13, 19) support the lowering of the CLSI and FDA susceptibility breakpoint for TZP against *Pseudomonas aeruginosa* and other

TABLE 5. PTA for parent regimen and dose-adjusted regimens

TZP dosing scheme	Probability of achieving 50% $fT >$ MIC at:					
	1 mg/liter	2 mg/liter	4 mg/liter	8 mg/liter	16 mg/liter	32 mg/liter
Traditional						
4.5 g i.v. every 6 h, 0.5-h infusion (CL_{CR} = 100 ml/min)	0.93	0.88	0.81	0.67	0.46	0.19
3.375 g i.v. every 6 h, 0.5-h infusion (CL_{CR} = 40 ml/min)	0.99	0.98	0.95	0.90	0.77	0.50
3.375 g i.v. every 6 h, 0.5-h infusion (CL_{CR} = 20 ml/min)	0.99	0.99	0.98	0.95	0.88	0.73
Extended infusion						
3.375 g i.v. every 8 h, 4-h infusion (CL_{CR} = 100 ml/min)	0.99	0.99	0.99	0.97	0.73	0.17
3.375 g i.v. every 12 h, 4-h infusion (CL_{CR} = 40 ml/min)	0.98	0.96	0.90	0.79	0.52	0.16
3.375 g i.v. every 12 h, 4-h infusion (CL_{CR} = 20 ml/min)	0.99	0.98	0.96	0.90	0.74	0.40



non-*Enterobacteriaceae* Gram-negative bacteria from ≥64 to ≥16 mg/liter.

The second aim was to determine the optimal renal dosage adjustments for the FDA-approved nosocomial pneumonia TZP dosing regimen and the extended-infusion TZP dosing regimen used at the Albany Medical Center Hospital. The goal was to identify the CL_{CR} breakpoint and dose adjustment for each of the regimens that would leave the PTA substantially unaltered and avoid causing profound accumulation. For extended-infusion TZP, the results support dose adjusting at a CL_{CR} of 20 ml/min. Extending the interval from every 8 h to every 12 h at a CL_{CR} of 40 ml/min resulted in a suboptimal PTA profile, especially for MICs of ≥8 mg/liter (Table 5). In contrast, dose adjustment at a CL_{CR} of 20 ml/min did not substantially alter the PTA profile (Table 5) and did not result in profound accumulation (Fig. 2D).

For the FDA-approved nosocomial pneumonia TZP dosing regimen (4.5 g TZP i.v. as a 30-min infusion every 6 h), a case can be made for either candidate renal dose adjustment regimen (3.375 g TZP i.v. for 30 min every 6 h at a CL_{CR} of 40 ml/min or 3.375 g TZP i.v. for 30 min every 6 h at a CL_{CR} of 20 ml/min). Both candidate renal dose adjustment schemes had an improved PTA profile compared to that of the parent regimen at a CL_{CR} of 100 ml/min (Table 5). However, the candidate regimen dose adjusted at a CL_{CR} of 20 ml/min had a more robust PTA for MICs of ≥16 mg/liter. The risk associated with waiting to dose adjust at a CL_{CR} of 20 ml/min was more accumulation: some subjects experienced an exposure ratio of greater than 4, although the majority of subjects had an exposure ratio of less than 3 (Fig. 2D). Given the wide safety window and lack of a clearly defined exposure-toxicity threshold, we recommend the candidate regimen dose adjusted at a CL_{CR} of 20 ml/min, especially when empirically or definitively treating serious Gram-negative infections with potentially higher MICs.

Several things should be noted when interpreting these results. First, this analysis included only three patients with CL_{CR} values of less than 40 ml/min. Since we previously demonstrated that piperacillin clearance in the presence of tazobactam is linear, we do not believe this to be a major issue (19). However, there are data that suggest that the clearance of piperacillin is nonlinear in patients with renal dysfunction, and it may compete with tazobactam for tubular secretion (2, 14, 25). While our model fits the data well, future piperacillin PK models should target patients with CL_{CR} values of less than 40 ml/min to test the validity of our PTA estimates. Until this is

FIG. 2. Distribution of AUC_{24SS} exposure ratios for various TZP dosing regimens. (A) Distribution of the AUC_{24SS} exposure ratio of 4.5 g every 6 h (30-min infusion) at a CL_{CR} of 40 ml/min relative to 4.5 g every 6 h (30-min infusion) at a CL_{CR} of 100 ml/min. (B) Distribution of the AUC_{24SS} exposure ratio of 4.5 g every 6 h (30-min infusion) at a CL_{CR} of 20 ml/min relative to 4.5 g every 6 h (30-min infusion) at CL_{CR} of 100 ml/min. (C) Distribution of the AUC_{24SS} exposure ratio of 3.375 g every 8 h (4-h infusion) at a CL_{CR} of 40 ml/min relative to 3.375 g every 8 h (4-h infusion) at a CL_{CR} of 100 ml/min. (D) Distribution of the AUC_{24SS} exposure ratio of 3.375 g every 8 h (4-h infusion) at a CL_{CR} of 20 ml/min relative to 3.375 g every 8 h (4 h infusion) at a CL_{CR} of 100 ml/min.

performed, the PTA and exposure ratios reported in this study should be viewed as conservative estimates.

Second, the K_{pc}/K_{cp} ratios (K_{cp}, transfer rate constant from the central compartment to the peripheral compartment; K_{pc}, transfer rate constant from the peripheral compartment to the central compartment) observed in this model are twofold higher than those of our previous publication, but we did not find this troublesome and the results were within reason. While similar, these were two distinct analyses. Clearance was modeled differently in this analysis, and this may contribute to the different ratios. Additionally, we included only 67% of the patients from our original publication in this analysis and added 12 patients with robust sampling. Collectively, we believe these differences most likely contribute to the observed differences in K_{pc}/K_{cp} ratios between publications.

In summary, we examined the effect of various levels of renal function on the PTA profile for traditional and extended-infusion TZP dosing strategies among hospitalized patients and found an inverse relationship between renal function and PTA. We used these data to determine the optimal candidate renal dose adjustment regimens for both the traditional and extended-infusion dosing schemes. For both regimens, the optimal candidate renal dose adjustment threshold was $CL_{CR} \leq 20$ ml/min. While the FDA-approved nosocomial pneumonia dosing regimen recommendation is to dose adjust at a CL_{CR} of 40 ml/min (1), we support our dose adjustment recommendation at the lower CL_{CR} of 20 ml/min due to an improved PTA profile and the lack of a clearly defined exposure-toxicity relationship. Consistently with previous PTA studies (13, 17, 21, 24), extending the infusion time greatly improved the pharmacodynamic profile of TZP, especially for MICs of $\geq$8 mg/liter. However, the PTA was suboptimal at 32 mg/liter for all intermittent and extended-infusion regimens evaluated. When the TZP MIC is 32 mg/liter, alternative agents should be considered. Because our findings are based on mathematical models, they should be validated in the clinical arena.

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