Population Pharmacokinetics of Ceftolozane/Tazobactam in Healthy Volunteers, Subjects With Varying Degrees of Renal Function and Patients With Bacterial Infections

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Abstract

Ceftolozane/tazobactam is a novel antipseudomonal cephalosporin and β-lactamase inhibitor in clinical development for treatment of complicated urinary tract (cUTI) and intra-abdominal (cIAI) infections and nosocomial pneumonia. The population pharmacokinetics of ceftolozane/tazobactam were characterized in healthy volunteers, subjects with varying degrees of renal function, and patients with cIAI or cUTI. Serum concentration data from 376 adults who received ceftolozane/tazobactam in doses ranging from 500 to 3000 mg were analyzed to identify factors contributing to the pharmacokinetic variability. Ceftolozane/tazobactam pharmacokinetics were well described by a linear two-compartment model with first-order elimination and moderate between-subject variability in both clearance and volume of distribution (Vc). For both ceftolozane and tazobactam, clearance was highly correlated with renal function with creatinine clearance influencing exposure, and infection influencing Vc. Body weight was an additional covariate affecting the Vc of ceftolozane. Other covariates tested, such as age, body weight, sex, ethnicity, and presence of infection, had no clinically relevant effects on exposure. The final pharmacokinetic models adequately described the plasma concentrations of ceftolozane and tazobactam and form the basis for further modeling and simulation including evaluation of probability of target attainment in a diverse population with varying demographics, degrees of renal function, and infection status.

Keywords

Ceftolozane/tazobactam is a novel antipseudomonal cephalosporin with a well-established β-lactamase inhibitor. In vitro studies have demonstrated potent activity against *Pseudomonas aeruginosa*, including drug-resistant strains, and other Gram-negative pathogens, including most common extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.[1–4] Ceftolozane exerts its bactericidal activity by inhibition of essential penicillin-binding proteins (PBPs).[5] Tazobactam is an inhibitor of most common class A β-lactamases and some class C β-lactamases that, by binding to the active site of these enzymes, protects ceftolozane from hydrolysis and broadens coverage to include most ESBL-producing Enterobacteriaceae.[4] In addition, ceftolozane/tazobactam has the most potent antipseudomonal activity among currently available cephalosporins[3] and is minimally affected by AmpC overexpression, increases in efflux mechanisms, and porin deficiencies.[6] Ceftolozane/tazobactam is currently in clinical development for the treatment of complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs), and nosocomial pneumonia.

The pharmacokinetic (PK) profile of ceftolozane/tazobactam has been studied in several preclinical and clinical studies.[7–10] In healthy volunteers, the PK of ceftolozane/tazobactam is dose-proportional and linear across a wide range of doses (up to 3000 mg/1500 mg as a single dose) with a terminal elimination half-life ($t_{1/2\beta}$) of approximately 2.5 hours for ceftolozane and 1 hour for tazobactam.[9] Both ceftolozane and tazobactam are primarily excreted in the urine; ceftolozane almost completely in the urine as unchanged parent drug, suggesting minimal metabolism, and tazobactam with 80% as the unchanged parent drug and the remaining as

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inactive M1 metabolite that is formed via hydrolysis of tazobactam.[9] There is no drug–drug interaction between ceftolozane and tazobactam when coadministered.[9]

PK/pharmacodynamic (PD) models are of particular importance for describing the efficacy and safety of antibacterials and for identifying patient covariates that need to be taken into account for determining optimal dose strategies and evaluating exposure–response relationships. The aims of this analysis were: (1) to develop a population PK model for ceftolozane/tazobactam in healthy subjects and in target populations such as patients with renal impairment and complicated bacterial infections; (2) to identify intrinsic and extrinsic determinants of variability (covariates) in the PK of ceftolozane and tazobactam. The analysis was performed using published guidance from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).[11,12]

Materials and Methods

A population PK analysis was performed on plasma ceftolozane and tazobactam concentration–time data from adult subjects enrolled in 10 studies. Subjects were included from multiple sites and all studies were performed in accordance with the International Conference on Harmonization guidelines on good clinical practice and the Declaration of Helsinki. An investigational review board approved the study protocols at each site.

Serum concentration data were analyzed from five studies in healthy volunteers (n = 184), three studies in subjects with varying degrees of renal impairment (n = 42), and two phase 2 studies in patients with bacterial infections (cUTIs [n = 73] and cIAIs [n = 77]). In all studies, ceftolozane was administered as a 1 hour intravenous infusion either alone or in combination with tazobactam at a fixed 2:1 ratio (ceftolozane: tazobactam). Healthy volunteers received single or multiple (every 8 hours [q8h] or every 12 hours [q12h]) doses of ceftolozane alone (250, 500, 1000, 1500, 2000 mg[13] (Cubist Pharmaceuticals. Data on file. 2009) or ceftolozane/tazobactam (500/250, 1000/500, 1500/ 750, 2000/1000, 3000/1500)[9,14,15] (Cubist Pharmaceuticals. Data on file. 2010) with sampling periods up to 24 hours following infusion (Table 1). Subjects with mild (creatinine clearance [CrCL] of ≥50 to <90 mL/min) or moderate (CrCL of ≥30 to <50 mL/min) renal impairment received a single dose of ceftolozane/tazobactam 1000/500 mg, with sampling up to 36 hours.[8] Subjects with severe renal impairment (CrCL of 15 to <30 mL/ min) received a single dose of ceftolozane/tazobactam 500/250 mg, with sampling up to 48 hours.[8] In the phase 2 trials, cUTI patients received ceftolozane alone 1000 mg (q8h)[16] and cIAI patients received ceftolozane/tazobactam 1000/500 mg (q8h).[17]

All subjects who received at least one dose of study medication and had at least one measurement of ceftolozane or tazobactam were included (N = 376). Plasma concentrations of ceftolozane and tazobactam were determined by a validated liquid-chromatography-tandem mass spectrometry assay (MicroConstants, Inc., San Diego, CA) described previously.[9] Concentrations below the limit of quantitation (BLQ), as defined previously,[9] were considered as missing. No substitutions were made to account for these missing data points.

Population Pharmacokinetic Analysis

Base model development. The model was developed in two stages. A preliminary PK model was developed based on datasets from three studies.[18] In the current analysis, the structural model was refined using the PK data from 10 studies (including patients with cUTI or cIAI) and the covariate analysis repeated. The results based on this revised model are presented here. A nonlinear mixed-effects model was developed with Phoenix® NLME™ software, version 1.2, 2012 (Certara L.P. Pharsight, St. Louis, MO) using first-order maximum likelihood estimation, and a two-compartment structure model was fitted to the plasma concentration–time data. The first-order conditional estimation-extended least squares (FOCE-ELS) engine was used for model fitting. The software R (R Foundation for Statistical Computing, Vienna, Austria, 2013) was used to generate tables of post hoc PK parameters and descriptive statistics.

Models had the form:

$$C_{P_{ij}} = C(D_i, t_j, \theta_i) + \varepsilon_{ij}$$

$$\theta_i = (\theta_{i1}, ..., \theta_{im})$$

where C_{pij} is the concentration at jth time for subject i, D_i represents dosing history for subject i, θ_i is the vector of m model parameters for subject i, and ε_{ij} is random error associated with a concentration at the jth time (t_j) for subject i.

A variance component, which assumed a log-normal distribution of PK parameters, was used to characterize the between-subject variability (BSV) and between-occasion variability (BOV) in model parameters using the following equation:

$$\theta_{in} = \theta_{TVn} exp(\eta_{in})$$

$$(\eta_1 ... \eta_m) \sim MVN(0, \Omega)$$

Where θ_{TVn} is the population typical value for the nth PK parameter (eg, clearance), and η_{in} is the individual random effect (η is referred to as ETA hereafter) and occasion random effect on the nth parameter for subject i that jointly follow a multivariate normal distribution (MVN) with mean zero and variance Ω.

Table 1. Summary of 10 Clinical Studies Included in the Population–Pharmacokinetic Analysis

Study	Phase	Population	N	Drug administration and dose
Ge 2010[13]	1	Healthy	48	IV Ceftolozane 250, 500, 1000, 1500, 2000 mg (single and multiple). Sampling up to 24 hours
Miller 2012[9]	1	Healthy	48	IV Ceftolozane/tazobactam 500/250, 1000/500, 1500/750, 2000/1000 mg (single and multiple). Sampling up to 24 hours; 10-day study
Cubist data on file 2010	1	Healthy	51	IV Ceftolozane/tazobactam 1000/500, 3000/1500 mg (single). Sampling up to 22.5 hours
Chandorkar 2012[14]	1	Healthy	25	IV Ceftolozane/tazobactam 1000/500 mg (multiple). Sampling up to 8 hours
Miller 2012[15]	1	Healthy	12	IV Ceftolozane/tazobactam 2000/1000 mg (multiple). Sampling up to 24 hours; 10-day study
Cubist data on file 2009	1	Normal and mild RI	12	IV Ceftolozane 1000 mg (single). Sampling up to 36 h
Wooley 2014[8]	1	Normal, mild and moderate RI	24	IV Ceftolozane/tazobactam 1000/500 mg (single). Sampling up to 36 hours
Wooley 2014[8]	1	Severe RI	6	IV Ceftolozane/tazobactam 500/250 mg (single). Sampling up to 48 hours
Umeh 2010[16] NCT00921024	2	cUTI	73	IV Ceftolozane 1000 mg (q8h). Sampling up to 6 hours
Lucasti 2014[17] NCT01147640	2	cIAI	77	IV Ceftolozane/tazobactam 1000/500 mg (q8h). Sampling up to 7 hours

cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections; ESRD, end-stage renal disease; IV, intravenous; RI, renal impairment; q8h, every 8 hours.

Residual unexplained variability was modelled using additive $\pm$ proportional error models, including:

$$y_{ij} = \hat{y}_{ij}(1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$$

Where y_{ij} (observed) and $\hat{y}_{ij}$ (predicted) represent the jth plasma drug concentration for the ith subject, and ε is the random residual variability. Each ε (ε_1 and ε_2) is normally distributed with mean 0 and variance σ^2.

Sources of Variability and Covariate Analysis

Sources of variability that may affect drug exposure were identified using correlation plots of individual random effects (ETA with mean 0 and estimated variance ω^2) of parameters such as systemic clearance (CL) and central volume of distribution (Vc) versus covariates. Extrinsic covariates analyzed included dose levels, drug–drug interactions between ceftolozane and tazobactam, and disease status (bacterial infections). Intrinsic covariates analyzed included body weight, age, sex, ethnicity, and baseline calculated CrCL. The CrCL was estimated using the Cockcroft–Gault formula:[19]

$$CrCL = \{[(140 - Age) \times WT]/S_{Cr}\}$$

where CrCL is creatinine clearance (mL/min), age is in years, WT is actual body weight (kg), and S_{Cr} is serum creatinine (mg/dL); for female subjects the value was multiplied by a factor of 0.85. Renal impairment was categorized as normal (CrCL $\geq$90 mL/min), mild (CrCL $\geq$50–<90 mL/min), moderate (CrCL $\geq$30–<50 mL/min), and severe (CrCL 15–<30 mL/min).

Scatter plots were used to examine the effect of continuous variables and box plots were used for categorical variables. The resulting graphs were screened using visual inspection, and the most statistically relevant covariates were retained and evaluated in the population PK model using an automatic stepwise forward additive–backward elimination approach to identify individual covariates that had a sufficient threshold effect based on the specified criteria ($P < 0.01$ for forward approach and $P < 0.001$ for backward approach). Covariates were introduced in a multiplicative order using a power model standardized by the median for continuous covariates and a linear model with an exponentiated factor relative to the reference for categorical covariates.

Final population PK model: evaluation and performance. The final population PK models for ceftolozane and tazobactam were evaluated using standard diagnostics, goodness-of-fit criteria, nonparametric bootstrap resampling, and visual predictive check (VPC). Final model selection was based on goodness-of-fit criteria evaluated using the log-likelihood difference between models, pertinent graphical representations of plasma concentrations (fitted, observed [individual dependent variable], population-predicted [PRED], and individual-predicted [IPRED]) versus time plots with assumption of log-normal distribution of PK parameters for BSV and BOV. Sensitivity of outliers was measured using conditional weighted residuals (CWRES) versus time or time after dose (for FOCE) plots. Shrinkage of individual random effects (ETA) toward the population mean was computed to assess whether the final model provided reliable estimates of individual PK parameters: Shrinkage = 1–(SD(ETA)/ω). SD(ETA) is the standard deviation of the

post hoc or empirical Bayesian estimates of ETA and ω is the population model estimate of the SD of ETA. Smaller shrinkage ≤0.2 indicates good individual estimates. A VPC was performed[20] to allow for comparisons of simulated and original data. The plasma concentration–time profiles of ceftolozane and tazobactam were simulated using 1000 replicates of the subject, and the median 90% prediction intervals (PI) were computed and compared with observed data. In addition, the robustness of the final population PK model was confirmed using nonparametric bootstrap resampling. The final model was fitted to a 1000 bootstrap dataset to obtain the median value of each PK parameter, along with the fixed-effect and random-effect parameters (interindividual variability and residual error). The nonparametric bootstrap values (median) for each parameter were compared with the original parameter estimates to examine bias and predictive error and were evaluated using 95% confidence intervals (CIs).

Results

Datasets

The population PK model included evaluable data from 376 adults who received ceftolozane and 243 who also received tazobactam, with 5048 observations for ceftolozane and 4249 observations for tazobactam. Demographic data stratified by presence or absence of infection are summarized in Table 2. Approximately, 39.9% (150/376) of subjects included in the PK model had an infection (cUTI or cIAI) and 32.2% (121/376) were renally impaired. Baseline CrCL was used to describe renal

function since serum creatinine was stable across the short treatment duration, with a median value of the actual changes (increase or decrease) of approximately 5% and a median value of the absolute changes of <15%; all changes were judged as not clinically meaningful. The age range of subjects was from 18 to 86 years.

Population Pharmacokinetic Model and Covariate Analysis of Ceftolozane

A two-compartmental structural model with a diagonal variance (omega) of CL, Vc, peripheral volume of distribution (Vp), and peripheral clearance (CL_2) fixed to a value of 0 provided the best data fit. The residual variability was found to be composite (both proportional and additive). Covariate analysis showed that both CL and Vc increased with body weight. A small negative trend between age and CL was also observed but it was not clinically meaningful. Both CL and Vc were significantly different for patients with an infection compared with healthy volunteers, and ceftolozane CL decreased as baseline CrCL decreased. Other covariates such as race, sex, dose level, and drug–drug interaction did not significantly affect CL or Vc of ceftolozane. The stepwise approach to identify significant covariates showed that the greatest improvement in the model included the effect of infection on both CL (<0.001) and Vc (<0.001), body weight on Vc (<0.001), and CrCL on CL (<0.001), with a significant difference between the minimum objective function value for the tested and base models [ΔMOF2] of −329.81; $P < 0.001$). The effects of renal impairment and infection status on ceftolozane CL are presented in a tornado plot (Figure 1A). The plot shows that between-

Table 2. Baseline Characteristics of Subjects Included in Population PK Model

Characteristic	Ceftolozane (n = 376)		Tazobactam (n = 243)	
	Phase 1, No Infection (n = 226)	Phase 2, Infection[a] (n = 150)	Phase 1, No Infection (n = 166)	Phase 2, Infection[b] (n = 77)
Men/women, n (%)	129 (57.1)/97 (42.9)	83 (55.3)/67 (44.7)	96 (57.8)/70 (42.2)	43 (55.8)/34 (44.2)
Race, white, n (%)	187 (82.7)	145 (96.7)	136 (81.9)	76 (98.7)
Age, y, mean (range)	44.7 (18–79)	53.5 (18–86)	43.7 (18–79)	47.0 (18–86)
Weight, kg, mean (range)	73.5 (49–106)	79.6 (43–173)	74.1 (49–106)	78.0 (50–145)
BMI, kg/m^{2} , mean (range)	25.8 (19–35)	27.3 (17–56)	26.0 (19–35)	26.6 (18–51)
Estimated CrCL, mL/min, mean (range)	101.0 (19–215)	97.4 (41–309)	100.4 (19–238)	105 (41–309)
Renal impairment,[c] n (%)				
None (normal)	186 (82.3)	69 (46.0)	137 (82.5)	48 (62.3)
Mild	28 (12.4)	78 (52.0)	17 (10.2)	26 (33.8)
Moderate	6 (2.7)	3 (2.0)	6 (3.6)	3 (3.9)
Severe	6 (2.7)	0 (0)	6 (3.6)	0 (0)

BMI, body mass index; CrCL, creatinine clearance; RI, renal impairment.
[a]Includes patients with cUTIs or cIAIs.
[b]Includes patients with cIAIs.
[c]CrCL ranges for normal, mild, moderate, and severe renal impairment were ≥90 mL/min, ≥50–<90 mL/min, ≥30–<50 mL/min, and 15–<30 mL/min, respectively. CrCL estimated by the Cockcroft–Gault formula.
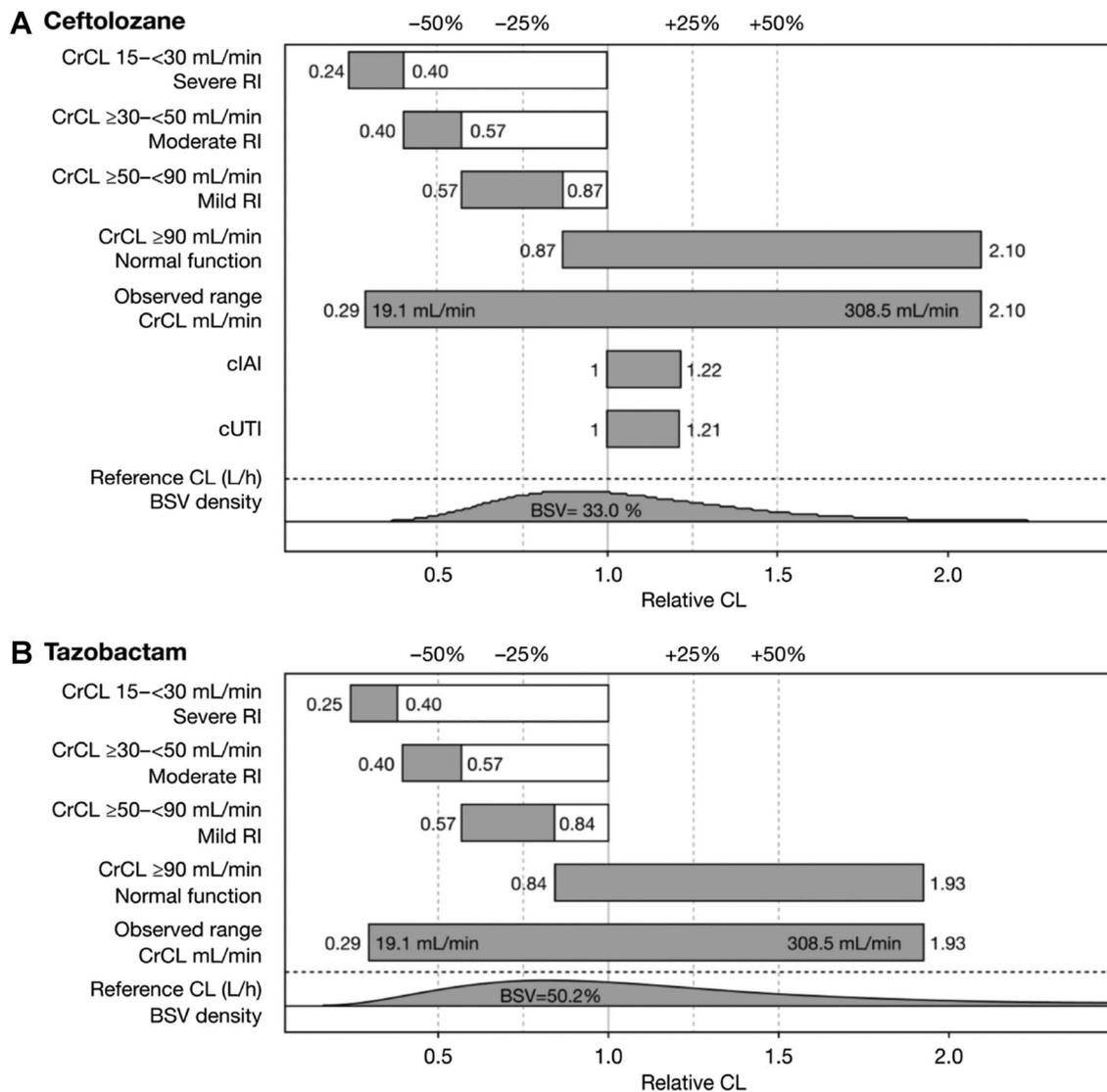
Figure 1. Tornado plot showing the effect of infection, renal impairment (based on CrCL categories over a standardized range) and BSV on the relative CL of [A] ceftolozane and [B] tazobactam. Numbers represent the CL range. BSV, between-subject variability; CL, clearance; CrCL, creatinine clearance.

subject variability (BSV 33.0%) had more impact on relative CL than the effect of infection (cIAI or cUTI). Furthermore, severe renal impairment and moderate renal impairment (based on CrCL categories over a standardized range of 19.1–308.5 mL/min) resulted in lower CL compared with normal and mild renal impairment.

The final model was further refined with infection status divided into cUTI and cIAI. Overall, the refined final model for ceftolozane was a two-compartment model with linear elimination including the effect of baseline CrCL on CL and body weight on Vc, and the effect of cUTI and cIAI infection on both CL and Vc. The population PK estimates, relative standard error (RSE), and BSV of the model are shown in Table 3A. In the final refined model, the Vc changed proportionally (linearly)

with body weight in subjects without cIAI. However, in cIAI patients, there was no significant correlation between Vc and body weight given the large observed variability. In addition, CL was similar in patients with cUTI and cIAI (6.18 and 6.23 L/h at CrCL = 109 mL/min), both about 20% higher than that in healthy subjects. Vc was about 30% different between these two patient groups (13.8 L at 74 kg body weight for cUTI and 18.2 L for cIAI). The inter-compartment clearance (CL_2) was about 1 L/h, while volume of distribution in the peripheral compartment was about 3 L. The parameter estimates of the final model were reliable with all standard error of measurement (SEM%) less than 50%, and the residual variability (ie, the sum of all variability that is not explained by the final model) was low, 16.8% for proportional error and

Table 3. Final Population–Pharmacokinetic Models Derived for [A] Ceftolozane and [B] Tazobactam

Parameter		Population estimates (RSE %)	BSV % (RSE %)	Shrinkage (%)
[A] Ceftolozane				
CL (L/h)	No infection	$5.11\ (2.15)*(CrCL/109)^{0.715\ (6.14)}$	33.0 (3.94)	3.5
	With cUTI	×1.21 (24.6)		
	With cIAI	×1.22 (22.5)		
Vc (L)	No infection	$11.4\ (2.70)*(weight/74)$	39.8 (4.50)	8.3
	With cUTI	×1.21 (30.1)*(weight/74)		
	With cIAI	×1.59 (12.3)		
CL$_2$ (L/h)		1.19 (2.24)	Fixed at 0	NA
Vp (L)		2.88 (fixed)	Fixed at 0	NA
Proportional error (%)		16.8 (11.8)	NA	NA
Additional error (µg/mL)		0.0524 (8.07)	NA	NA
[B] Tazobactam				
CL (L/h)		$18.0\ (3.39)*(CrCL/115)^{0.67\ (11.1)}$	50.2 (4.98)	4.68
Vc (L)	No infection	14.2 (4.45)	52.5 (6.14)	11.5
	With cIAI	× 1.47 (21.9)		
CL$_2$ (L/h)		3.13 (4.59)	Fixed at 0	NA
Vp (L)		4.29 (2.61)	Fixed at 0	NA
Proportional error (%)		26.0 (1.64)	NA	NA

BSV, between-subject variability; CL, clearance; CL$_2$, peripheral clearance; CrCL, creatinine clearance; IAI, intra-abdominal infection; NA, not applicable; RSE, relative standard error; UTI, urinary tract infection; Vc, central volume of distribution; Vp, peripheral volume of distribution.

0.05 µg/mL for additive error. For a fitted ceftolozane concentration of 100 µg/mL, the total residual error would be 16.85 µg/mL.

Diagnostic plots showed a good fit of the final model to ceftolozane plasma concentrations (Figure 2A). Individual observed and PRED plasma concentrations were symmetrically distributed, and CWRES versus PRED were homogenously distributed around 0 with 25 PK samples from 20 subjects displaying CWRES > 4, suggesting no bias in predictions relating to low or high ceftolozane concentrations. Outliers (CWRES > 4) were not excluded from the analysis, as they did not have a significant effect on PK parameters (difference range: −0.2% to 6.7%) and the changes in BSV of CL and Vc were less than 31%. VPC simulations were within the 90% PI of the predicted median across all doses. Similarly, differences in PK parameters and covariate effects between the final model and bootstrap runs were <5%.

Population Pharmacokinetic Model and Covariate Analysis of Tazobactam

The best-fit model for tazobactam was structurally similar to that for ceftolozane, a two-compartmental structural model with a diagonal variance (BSV) for CL and Vc and a proportional model for unexplained residual variability. Similar to ceftolozane, in the covariate analysis differences in both CL and Vc were observed between subjects with and without infection, and there was a strong correlation between tazobactam CL and renal impairment category (ie, decrease in CL with decreasing baseline CrCL). The stepwise approach to identify significant covariates showed that the greatest improvement in the model included the effect of cIAI infection on Vc (note there were no tazobactam data from cUTI patients) and of CrCL on CL (ΔMOF2: −92.84; $P < 0.001$). The ΔMOF2 was −103.02 ($P = 0.001$) when the effect of cIAI infection was included in the model and −109.73 ($P = 0.01$) when the effect of weight on Vc was also included. No trends were noted between other covariates tested and tazobactam PK.

The final model was confirmed to be a two-compartmental model with linear elimination that included the effect of baseline CrCL on CL showing a power function of 0.67 (ie, $[CrCL/115]^{0.67}$) and the effect of infection on Vc. In this model, the population estimates (RSE%) derived for tazobactam were 18.0 L/h (3.39) for CL, 14.2 L (4.45) for Vc in subjects without infection, 3.13 L/h (4.59) for CL$_2$ (inter-compartment clearance), and 4.29 L (2.61) for Vp (Table 3b). The parameter estimates of the final model were reliable with all SEM% less than 50%, and a proportional unexplained error of 26.0% (1.64), although the BSV was higher (50.2% for CL and 52.5% for Vc). The tornado plot shows that, similar to ceftolozane, severe and moderate renal impairment resulted in lower CL of tazobactam compared with normal and mild renal impairment (Figure 1B).

The model was robust showing a good fit to plasma concentrations of tazobactam (Figure 2B) and CWRES versus PRED were homogenously distributed around 0 with 17 PK samples from 13 subjects displaying CWRES > 4 and nonexclusion of outliers (difference range: −2.8% to 7.7%). However, when outliers were excluded the BSV of CL and Vc decreased by 42.5% and 32.5%, respectively. VPC simulations were within 90% PIs of predicted

A Ceftolozane
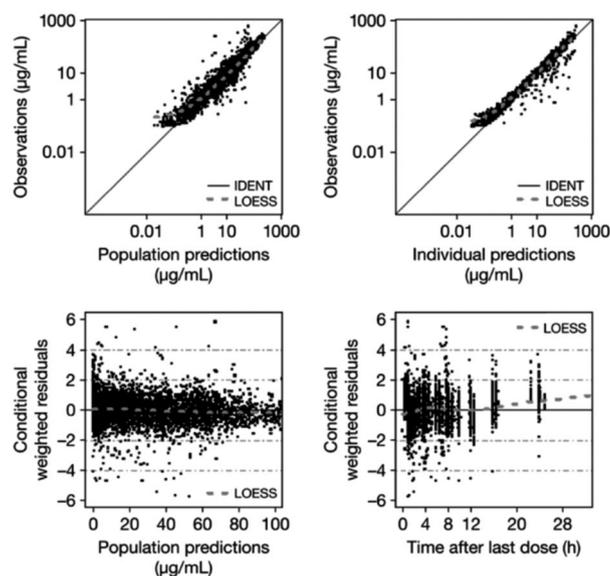
B Tazobactam
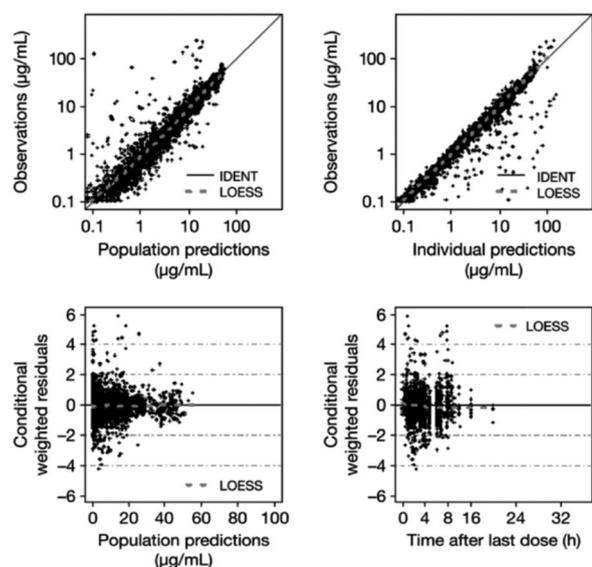
Figure 2. Population and individual predicted versus observed plasma concentrations of [A] ceftolozane and [B] tazobactam for the final PK model (goodness-of-fit plot). IDENT, identity line; LOESS, locally weighted scatter smoothing.

medians and differences in bootstrap resampling analysis were <4% compared with the final model.

Discussion

This is the first report describing the population PK of ceftolozane/tazobactam in distinct populations, including those with varying degrees of renal impairment and patients with cUTIs and cIAIs. Using data from phase 1

and phase 2 studies, the effects of various covariates on the PK model were assessed to identify sources of individual variability in the PK of ceftolozane/tazobactam. For both ceftolozane and tazobactam, plasma concentration–time data were best fitted using a two-compartmental model with first-order elimination, with a moderate BSV in both clearance and volume of distribution; this model was shown to be robust using all standard diagnostic and goodness-of-fit criteria. The goodness-of-fit plots were homogenously distributed suggesting no bias in the predictions of high and low drug concentrations and VPC simulations were within the 90% PI of the predicted median across all doses, indicating that the ceftolozane/tazobactam population PK models will accurately predict plasma concentration–time data over a wide dose range. Both models had a low residual variability (proportional error) indicating that they would be accurate in the majority of samples and useful for further PK/PD analyses.

In the model for ceftolozane that included patients with cUTI or cIAI, a total of 63 scenarios with various combinations of covariates were evaluated for their effect on the CL and Vc of ceftolozane. As expected, CrCL (renal function) was found to be the most significant covariate explaining the variability of CL. The presence of infection also appeared to influence CL, but for the same CrCL, the influence of infection on CL was not clinically meaningful. Body weight and presence of infection were the most important factors explaining the variability of Vc. The model is well interpretable as CrCL is expected to be a major covariate since ceftolozane is almost exclusively eliminated by the kidneys.[9,13] The final equation for CL in the population PK model of ceftolozane was: $CL_{of\ ceftolozane} = 5.11\,L/h * (CrCL/109)^{0.715}$ with a multiplicative factor of 1.21 for patients with cUTI and 1.22 for patients with cIAI. This model indicates that CL would change by about 15% for every 20% change (increase or decrease) in CrCL and by about 20% in both cUTI and cIAI patients. The effect of body weight on Vc is also physiologically interpretable, as ceftolozane is distributed by diffusion into extracellular fluids, so volume may increase with an increase in body weight.[9] The final equation for Vc of ceftolozane was: $Vc_{of\ ceftolozane} = 11.4\,L \times (WT/74\,kg)$ with a multiplicative factor of 1.21 for patients with cUTI and 1.59 for patients with cIAI. Vc would be expected to change by about 20% for every 20% change (increase or decrease) in body weight except in cIAI patients, where volume was not a function of weight and where the cIAI effect was increasing it by factor of 1.50-fold. For example, with a typical body weight of 74 kg, Vc would be about 11, 14, and 18 L in healthy subjects, cUTI patients, and cIAI patients, respectively. The effect of cIAI on Vc and CL is consistent with other β-lactam antibiotics showing that intra-abdominal disease may cause changes in PK

including faster antibiotic clearance and significant increase in Vc.[21] Overall, the population PK model for ceftolozane was stable, reliable, and interpretable. The estimated random BSV of 33% and 40% in CL and Vc, respectively, is not unreasonable in such a heterogeneous population and the estimated residual variability of 17% is within the typical range of bioanalytical variability and other unknown sources of variability.

In the model for tazobactam, which included patients with cIAI, a total of 50 covariate scenarios were evaluated for their effect on the CL and Vc of tazobactam. Renal function and infection were the most important factors explaining the variability of CL and Vc, respectively. Again the model is well interpretable as CrCL is expected to be a major covariate since tazobactam is primarily eliminated by the kidneys[9] and the presence of intra-abdominal disease has been shown to increase Vc.[21] The final equations for CL and Vc of tazobactam were: $CL_{of\ tazobactam} = 18.0\,L/h * (CrCL/115)^{0.67}$ and $Vc_{of\ tazobactam} = 14.2\,L$ with a multiplicative factor of 1.47 for patients with cIAI. In this model, a 20% change of CrCL from the central value of 115 mL/min would increase or decrease tazobactam CL by 13% to 14% and the Vc of tazobactam is about 47% larger in cIAI patients than in healthy subjects. Similar to the model for ceftolozane, the final PK model for tazobactam is stable, reliable, and interpretable. The estimated random BSV in CL and Vc were about 50% and 53%, respectively, not unexpected in a very heterogeneous population. The estimated residual error (including bioanalytical variability) was approximately 26%, suggesting a relatively high variability from unidentified sources in addition to the bioanalytical variability.

As anticipated for primarily renally eliminated drugs, renal function (as measured by CrCL) was the most significant covariate influencing the PK of ceftolozane/tazobactam, and drug clearance decreased substantially with increasing impairment. Animal infection models have shown that, similar to other cephalosporins, the therapeutic efficacy of ceftolozane is best correlated with the percentage of time the plasma drug concentration exceeds the MIC for the target organism ($\%T > MIC$).[7] Similarly, the PD driver for tazobactam is thought to be the percentage of time above a threshold concentration ($\%T > threshold$).[10,22] As renal impairment increases the $\%T > MIC$ for renally cleared antibiotics such as ceftolozane/tazobactam, it is important to conduct PK/PD modeling in order to ensure that renally impaired patients are not exposed to excessive drug concentrations, and that PK/PD targets predictive of favorable outcomes are achieved. Based on the population PK model, there was no clinically meaningful difference (ie, relative difference <25%) in CL between the subjects with normal renal function and those with mild renal impairment indicating that dose adjustment is not warranted in subjects with mild renal impairment. However, moderate to severe renal impairment substantially affected the CL of both ceftolozane and tazobactam suggesting that a dose reduction may be warranted in these patients.

While infection was an important covariate explaining the variability in CL and Vc for ceftolozane and Vc for tazobactam, its effect on steady-state PK parameters (eg, area under the plasma concentration–time curve at steady state [AUCss]) was not considered clinically meaningful as any exposure changes were limited to less than 20%. Furthermore, Vc does not directly affect AUC since AUC is driven by CL. For a typical patient with bacterial infection (ie, CrCL >90 mL/min and body weight 74 kg), the geometric mean estimate of the $t_{1/2\beta}$ was approximately 3 hours (2.71 hours for cUTI and 2.72 hours for cIAI patients) for ceftolozane and 2 hours for tazobactam and similar to that in subjects without infection, suggesting that $t_{1/2\beta}$ of ceftolozane/tazobactam is not expected to change in patients with a bacterial infection. Although slightly elevated tazobactam AUCss were seen in patients with bacterial infection and mild renal impairment, this increase of exposure was most likely associated with the infection since no difference in AUCss was observed for patients with bacterial infection and moderate renal impairment.

Body weight was a statistically significant covariate for ceftolozane volume of distribution, but did not influence exposure alone in a clinically meaningful manner. Other covariates such as sex, age, race, and dose levels did not appear to have clinically relevant direct impact on the PK profiles of ceftolozane/tazobactam. Furthermore, similar to previous observations,[9] no drug–drug interaction was observed between ceftolozane and tazobactam and the PK profile of ceftolozane was unaffected by administration of tazobactam.

This analysis has some limitations. There are a number of assumptions relating to normality of random effects and structure of variance.[23] Also, patients with other types of infections were not included, and it may be important to identify any additional covariates to extrapolate the results to other infections, such as nosocomial pneumonia.[24,25] However, given that the PK of ceftolozane/tazobactam is dose-proportional and linear and that CrCL is the most important covariate of exposure, the model theoretically can be adapted to other infections. This approach is supported by data from a randomized, double-blind, placebo-controlled, phase 1 study demonstrating the dose proportional and linear PK of ceftolozane/tazobactam when administered as a 3 g dose in healthy volunteers.[15]

In summary, this analysis conducted by combining PK data across a range of subjects provided a comprehensive, stable, and interpretable model explaining the determinants of variability in the disposition of ceftolozane/tazobactam. The final PK models adequately described

the plasma concentrations of ceftolozane and tazobactam and form the basis for evaluation of the probability of target attainment in a diverse population with varying demographics and degrees of renal impairment. For both ceftolozane and tazobactam, which are primarily renally eliminated, clearance was influenced by renal function. Other covariates tested, such as age, body weight, sex, ethnicity, and presence of infection, had no clinically relevant effects on clearance. The model can be utilized to further support optimal dosing scenarios to maximize efficacy and safety of ceftolozane/tazobactam for treatment of serious bacterial infections in subjects with varying degrees of renal impairment. Monte Carlo simulations derived with the population PK/PD model can also be utilized to further guide dosing recommendations for ceftolozane/tazobactam in various populations, for different pathogens of interest, and for other indications such as nosocomial pneumonia infection.

The expanding antimicrobial resistance among Gram-negative pathogens causing serious infections has necessitated the development of new antimicrobials. In vitro studies have shown that ceftolozane has the most potent antipseudomonal activity among currently available cephalosporins, and the addition of tazobactam broadens coverage to include the most common ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, and other Enterobacteriaceae.[2,3] These data, together with the results of this population PK analysis, suggest that ceftolozane/tazobactam can provide clinicians with a potential alternative to the currently recommended antimicrobials for the empiric treatment of cIAIs and cUTIs in patients with varying degrees of renal function, especially when resistant Enterobacteriaceae or *P. aeruginosa* are suspected.

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