Pharmacokinetics of Ceftolozane/Tazobactam in Patients with Burns

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BACKGROUND

Antimicrobial dosing in moderate/severe burns patients is complicated due to the potential unpredictable hyperdynamic pathophysiologic states including 1) hypoproteinemia, 2) acute kidney injury and 3) onset of septicemia. Therefore, distribution assumptions about the population pharmacokinetic (PopPK) profiles of either endogenous or xenobiotic pharmacophores in this patient population can lead to biased parameter estimates. In order to prevent potential bias an agnostic nonparametric adaptive grid approach to describe ceftolozane/tazobactam (C/T) PopPK profiles in patients with partial- and full-thickness burns was employed.

METHODS

Patients population and study design.
This was a single-center study, open-label, fixed-dose and single group assignment pharmacokinetics study with 6 subjects (5 males and 1 female), aged between 18 to 80 years with >/=20% of total body surface area (BSA) burnt, targeted for enrollment (ClinicalTrials.gov Identifier: NCT03002506). The study was approved by Texas Tech University Health Sciences Center Institutional Review Board (IRB# A17-4015). All enrolled subjects provided written informed consent.

Patients needed to have central venous or arterial line access prior to study enrollment. The exclusion criteria were: pregnant or lactating women, body weight <60kg or >130kg, blood donation within 8 weeks, vasopressor agents or ceftolozane/tazobactam within 48hours, history of penicillin or beta-lactam allergies, abnormal liver function tests (5 times the upper limit for the laboratory), or creatinine clearance <30mL/min, based on the Cockcroft-Gault equation. There were no racial/ethnicity or language barriers attached to the recruitment criteria.

Blood sampling.
Ceftolozane/Tazobactam 2gram/1gram dose was administered via 60-minute intravenous infusions. Thereafter, serial blood samples were obtained at the following time points: 0 (pre-dose) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours following the start of infusion for determination of plasma drug concentrations. These intensive sampling times were chosen to provide the concentration-time data over an entire 24-hour dosing interval for both ceftolozane and tazobactam.

Determination of ceftolozane/tazobactam concentrations.
Both ceftolozane and tazobactam plasma concentrations were determined by a validated high performance liquid chromatography (LC)-tandem mass spectrometric (MS/MS) assays. (PMID: 32905989)

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METHODS (CONT.) AND RESULTS

Population pharmacokinetic analysis.
Population pharmacokinetic modeling was performed using NPAG algorithm with the Pmetrics package for R (version 1.5.2)(18-20). One-, two- and three-compartments structural models were initially examined without covariates to determine best fit and to obtain parameter estimates. Akaike information criteria (AIC) was used to examine goodness-of-fit and the select the optimal or most-likely model. Additionally, population bias were calculated. Individual and population plots of observed concentrations versus predicted concentrations, together with weighted residual versus time, were used in selecting the final model the best represented the data. Lower AIC values and uniformly distributed residuals indicated the better-fitting model.

The relationships between model parameters and the different covariates examined (age, sex, CrCL, %BSA burnt, weight, height, BMI) were similarly examined iteratively using linear, nonlinear regression, allometric scaling and assessment of visual plots. The influence of renal function related covariates, specifically weight and CrCL, was tested against Ke, Ka and V using linear models [Y= C + (CrCL/CrCLmedian)X], exponential models [Y=C + e(CrCL/CrCLmedian)x], and allometric models [Y=C + (CrCL/CrCLmedian)0.75X]. CrCL represented median CrCL in the data. Covariates which reduced population bias and improved model precision were integrated into the final model.

Assay error and other environmental noise were modeled using the polynomial equation:
C0 + C1x[obs] + C2x[obs]2 + C3x[obs]3, where [obs] is the observed concentration error. Additive and multiplicative error models were examined with observations weighted by (λ2 + SD2)0.5 and SD x γ, respectively, where λ and γ represent process noise, such as sampling uncertainty and model misspecification, with %CV of up to 40% tested

Table 1: Baseline demographic and clinical characteristics of patients

Characteristic, (units)	Number, n (%)	Mean	SD	Median	Range
Sex					
Male	5 (83%)				
Female	1 (17%)				
Age (years)		42.67	13.91	42	24-66
Weight (kg)		85.93	11.54	85.15	74.80-99.10
Height (cm)		171	12.80	172	155-191
BMI (kg/m^2)		30.19	8.17	28.38	21.46-41.28
CRCL (mL/min)		105.83	28.11	103.5	73-148
BUN (mg/dL)		25.33	4.63	24.5	21-34
Total protein (g/dL)		4.4	0.24	4.35	4.1-4.8
Albumin (g/dL)		2.25	0.24	2.35	1.9-2.5
AST (u/L)		33.67	15.13	30.5	16-56
ALT (u/L)		37.17	13.88	35.5	22-61
ALP (IU/L)		43.5	10.46	41	32-59
WBC count (x10^9/L)		13.61	5.58	11.87	7.69-19.42
Hemoglobin (g/dL)		9.38	1.55	9.5	7.7-11.9
Hematocrit (%)		30.02	4.05	29.5	24.2-36.6
Platelet count (x10^9/L)		302	185	219	181-658
Burns Stage					
Partial thickness	1 (17%)				
Full thickness	5 (83%)				
Days from burns		10.27	3.24	10.15	5.7-14
% BSA burnt		43.67	14.98	38	27-66
Prior systemic antibiotic	4 (67%)				
Cefepime	2 (33%)				
Ceftriaxone	1 (17%)				

Figure 1. Ceftolozane and tazobactam plasma concentrations

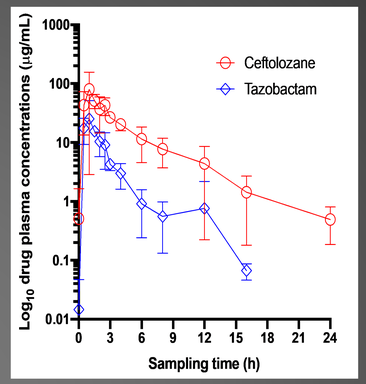
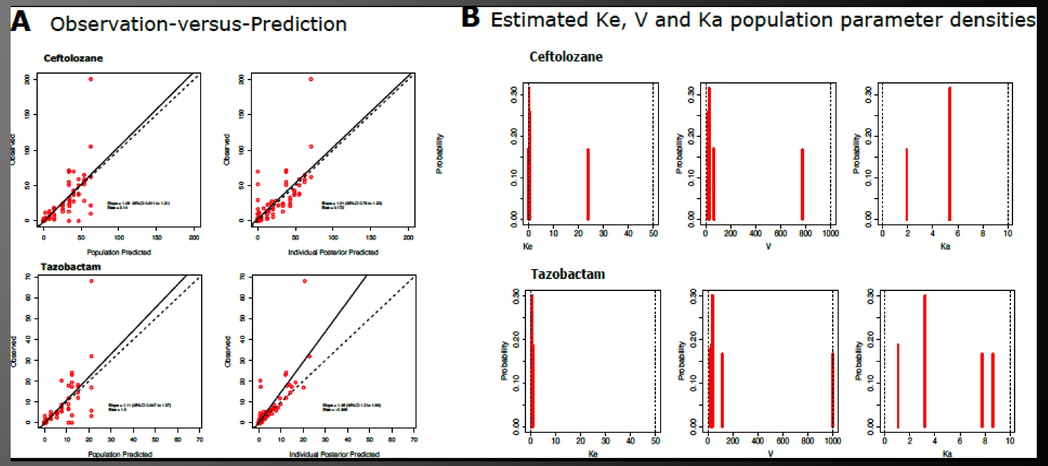


Table 2: PK Parameter Estimates

Parameter	Mean	SD	%CV	Median	%Shrinkage
Ceftolozane					
Ke	4.232	8.760	206.994	0.375	0.001
V	157.610	275.586	174.853	28.956	0.006
Ka	4.785	1.283	26.807	5.355	0.003
Tazobactam					
Ke	0.649	0.253	38.939	0.567	6.022
V	206.158	356.305	172.831	38.555	0.007
Ka	20.459	15.279	74.681	15.973	1.531

Figure 2.A Observed-versus-predicted goodness-of-fit plots

Figure 2.B Distribution of the population pharmacokinetic parameters of ceftolozane and tazobactam



CONCLUSION

Ceftolozane/Tazobactam exhibited high variability surpassing that observed with severe infections, suggesting that dose adjustment and/or therapeutic drug monitoring may be needed to balance target attainment from dose-related toxicities.

ACKNOWLEDGEMENTS

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