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O1065 Population pharmacokinetics of unbound ceftolozane and tazobactam in critically ill patients without renal dysfunction

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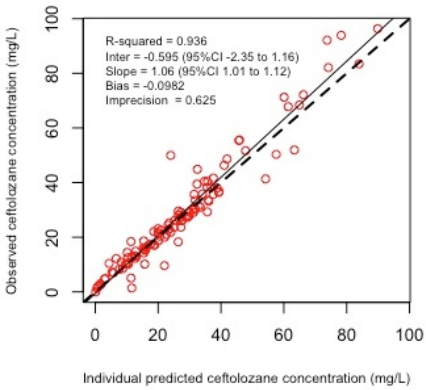
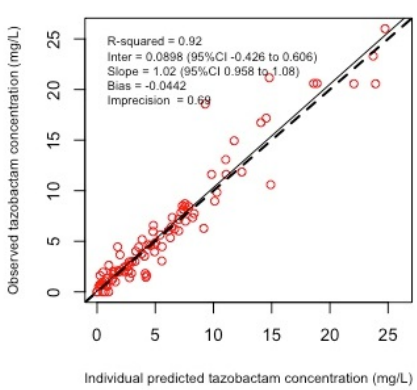
Background: Ceftolozane-tazobactam is a newly available antibiotic with little data available to guide dosing in critically ill patients. This study aimed to describe the population pharmacokinetics of unbound ceftolozane and tazobactam concentrations and assess the appropriateness of doses recommended for critically-ill patients without renal dysfunction.

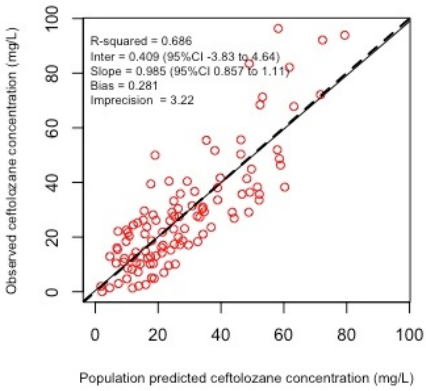
Materials/methods: In a prospective observational study, adult (≥ 18 years) critically ill patients without renal dysfunction were enrolled if diagnosed with systemic infection with known or presumed susceptibility to ceftolozane/tazobactam. Patients were treated with 1/0.5g or 2/1g ceftolozane/tazobactam given eight-hourly (q8h). Serial plasma samples were collected during one dosing interval for unbound concentration measurement by UHPLC-MS/MS. A non-parametric population pharmacokinetic analysis was performed using Pmetrics® in R, with subsequent Monte-Carlo dosing simulations (n=1000) to estimate the probability of target attainment of 40% and, a more aggressive, 100% time above MIC ($fT_{>MIC}$). The fractional target attainment (FTA) was estimated based on the EUCAST MIC distribution for *Pseudomonas aeruginosa*.

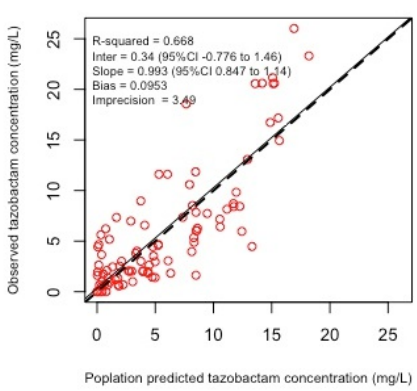
Results: Twelve patients (7 female) with median (IQR) weight 80 (64-99) kg, albumin concentration 23 (18-25) g/L and urinary-creatinine clearance 107 (75-147) mL/min, were enrolled. A two-compartment model adequately described the unbound concentration-time data for ceftolozane and tazobactam. Body weight and albumin were included as covariates on volume of the central compartment (Vc) for both drugs. Mean (SD) parameter estimates were clearance 9.8(5.8) L/h and 32.8 (12) L/h; Vc 12.8 (5.6) L and 19.4 (7) L for ceftolozane and tazobactam respectively. For empiric therapy (includes MICs <64 mg/L) the 3g q8h dose resulted in a significantly higher FTA than the 1.5g q8h dosing for the 100% $fT_{>MIC}$ target. The continuous infusion regimen (loading dose of 1.5g followed by 4.5g/24h continuous infusion) also achieved a high FTA for the 100% $fT_{>MIC}$ target. For directed therapy against susceptible pathogens (MIC <4 mg/L) the 3g q8h regimen appears adequate to achieve 40% $fT_{>MIC}$ exposure.

Conclusions: For empiric treatment initiation, 3g q8h is appropriate for achievement of target exposures for critically ill patients without renal dysfunction. Alternative dosing regimens, including continuous infusion, may also be useful for higher MIC pathogens.


R-squared = 0.936
Inter = -0.595 (95%CI -2.35 to 1.16)
Slope = 1.06 (95%CI 1.01 to 1.12)
Bias = -0.0982
Imprecision = 0.625
Observed ceftolozane concentration (mg/L)
Individual predicted ceftolozane concentration (mg/L)


R-squared = 0.92
Inter = 0.0898 (95%CI -0.426 to 0.606)
Slope = 1.02 (95%CI 0.958 to 1.08)
Bias = -0.0442
Imprecision = 0.69
Observed tazobactam concentration (mg/L)
Individual predicted tazobactam concentration (mg/L)


R-squared = 0.686
Inter = 0.409 (95%CI -3.83 to 4.64)
Slope = 0.985 (95%CI 0.857 to 1.11)
Bias = 0.281
Imprecision = 3.22
Observed ceftolozane concentration (mg/L)
Population predicted ceftolozane concentration (mg/L)


R-squared = 0.668
Inter = 0.34 (95%CI -0.776 to 1.46)
Slope = 0.993 (95%CI 0.847 to 1.14)
Bias = 0.0953
Imprecision = 3.49
Observed tazobactam concentration (mg/L)
Poplation predicted tazobactam concentration (mg/L)