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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

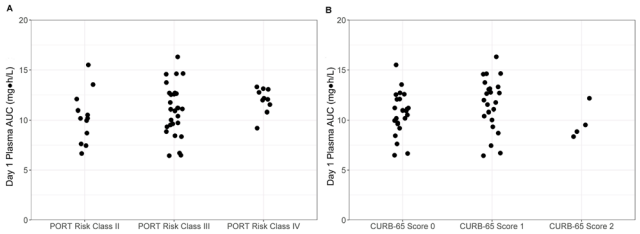
Background. Omadacycline is a novel aminomethylcycline with activity against Gram-positive and -negative organisms, including tetracycline-resistant pathogens. Omadacycline was recently approved in the United States for treatment of adult patients with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections. Analyses were undertaken to determine whether PORT risk class and CURB-65 score influence the pharmacokinetics of omadacycline in patients with CABP.

Methods. Omadacycline pharmacokinetic data were available from omadacycline-treated patients with CABP enrolled in the Phase 3 OPTIC Study. Patients received omadacycline 100 mg IV q12h on Day 1 followed by 100 mg IV q24h. After Day 3, patients could be switched to 300 mg PO q24h if predefined clinical stability criteria were met. Four pharmacokinetic samples per patient were collected between Days 2 and 5. These data were previously utilized in the development of a population pharmacokinetic model describing the disposition of omadacycline [Microbe 2018; Abstr SAT-628]. Individual post-hoc parameter estimates for patients enrolled in the OPTIC study were utilized to compute Day 1 total-drug plasma area under the concentration-time curve (AUC) values following administration of omadacycline 100 mg IV q12h. Differences among these AUC values by PORT risk class and CURB-65 score were assessed using a one-way ANOVA.

Results. A total of 187 pharmacokinetic samples were available from 50 patients. Among the patients classified as PORT risk class II, III, and IV (n = 12, 28, and 10, respectively), mean Day 1 omadacycline AUC values were 10.2, 11.0, and 12.0 mg L/h, respectively. Among patients with CURB-65 scores of 0, 1, and 2 (n = 23, 23, and 4, respectively), mean Day 1 omadacycline AUC values were 10.6, 11.6, and 9.7 mg L/h, respectively. The differences in mean AUC values were not statistically significant among patients by PORT risk class (P = 0.248) and CURB-65 score groups (P = 0.745). Moreover, variability was similar across these groups as displayed in Figure 1.

Conclusion. Omadacycline exposures were similar across PORT risk class and CURB-65 score groups; thus, omadacycline dose adjustments based on these classifications are likely not warranted.

Figure 1. Day 1 omadacycline total-drug plasma AUC by PORT risk class (A) and CURB-65 score (B)



Disclosures. **All authors:** No reported disclosures.

1562. Safety and Efficacy of High-Dose Cefazolin Therapy in Obesity
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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. Obesity leads to altered pharmacokinetics through changes in volume of distribution and clearance, which can impact antimicrobial dosing. Although there is data to support higher cefazolin pre-operative dosing for surgical prophylaxis, data evaluating treatment doses of cefazolin in obese patients is lacking. This study was designed to assess the safety and efficacy of high-dose (HD) cefazolin compared with traditional-dose (TD) cefazolin in obesity.

Methods. This was a multicenter, retrospective, cohort study of patients admitted from September 1, 2013 to August 31, 2018. Obese adults, defined as a BMI > 30 kg/m^2, receiving cefazolin for at least 48 hours for bacteremia or skin and soft-tissue infection were eligible for inclusion. Patients with creatinine clearances <30 mL/minute or positive MRSA cultures were excluded. TD cefazolin was defined as 1–2 g IV every 8 hours and HD cefazolin was defined as 2 g every 4–6 hours. Patients were matched 1:1 based on indication, severity of illness, and BMI. Primary objective was to compare rates of treatment-emergent adverse events (TEAE). Secondary outcomes included comparison of treatment failure rates and 30-day readmission.

Results. A total of 332 patients (166 matched pairs) were included in this analysis. Baseline demographics were similar between groups with the exception of higher age in the TD group (61.8 TD vs 55.1 HD; P < 0.001) and more males in the HD group (39.2% TD vs. 65.6% HD; P < 0.001). Median Charlson comorbidity index was also higher in the TD group [4 (2–6) TD vs. 3 (1–4) HD; P < 0.001]. There were no differences in TEAE between groups (24.1% TD vs. 16.9% HD; P = 0.103). Treatment failure occurred more frequently in the TD group (24.7% TD vs. 15.1% HD; P = 0.028), driven primarily by rates of readmission secondary to recurrence or relapse of the index infection (18.7% vs. 11.5%; P = 0.07).

Conclusion. There were no differences in TEAE in patients who received TD cefazolin vs. HD cefazolin therapy. Obese patients receiving TD therapy experienced higher treatment failure than those receiving HD therapy. Dose-optimization strategies with cefazolin in obese patients should be further explored.

Table 1: Adverse Events

	Traditional-Dose (n = 166)	High-Dose (n = 166)	p-value
TEAE	40 (24.1%)	28 (16.9%)	0.103
TEAE leading to discontinuation	4 (2.4%)	5 (3%)	1.000
Hematologic	12 (7.2%)	7 (4.2%)	0.237
Gastrointestinal	24 (14.4%)	12 (7.2%)	0.034
Acute kidney injury	10 (6%)	2 (2.7%)	0.019
30-day *C. difficile* infection	4 (2.4)	0 (0)	0.123

Disclosures. **All authors:** No reported disclosures.

1563. Population Pharmacokinetics and Pharmacodynamics of Daily and Extended Interval Dalbavancin Dosing Regimens for Salvage Therapy of *Staphylococcus aureus* Endocarditis: Mechanistic Modeling of Rabbit Infection Data to Support Human Dosing Regimens
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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

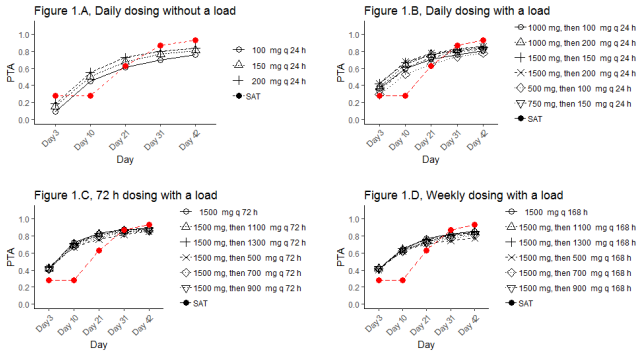
Background. Dalbavancins' (DAL) long half-life and favorable susceptibility profile makes it an attractive option for salvage therapy for endocarditis caused by *Staphylococcus aureus* (SA), including those with elevated vancomycin (VAN) MIC. The aim of our study was to establish the PKPD of DAL based on a rabbit model of infection and extrapolate those results to the design of human treatment regimens.

Methods. Data from a rabbit endocarditis model of SA with VAN MICs of 2 and 8 mg/L were fitted using an inoculum-size dependent model and the Pmetrics software. Then, the results were linked to a human PK model to simulate regimens with or without a loading dose. Probability of target attainment (PTAs) for achieving bacterial density of <2 log CFU per gram of vegetation was compared with outcomes based on standard antibiotic therapy (SAT) at 3, 10, 21, 31, and 42 days.

Results. Mean (SD) PTAs of 34.3% (10.5%), 61.3% (7.0%), 73.5% (5.4%), 79.5% (4.3%), and 83.1% (3.4%) were estimated for all regimens combined with maximum PTAs of 41.8%, 63.6%, 77.8%, 86.6%, and 88.9% for the highest weekly dose at 3, 10, 21, 31 and 42 days of therapy, respectively. While all approaches should achieve an adequate probability of clearing of the colonies by day 21, only doses near 2,000 mg/week are likely to approximate sterilization rates similar to that expected by the SAT at day 42. We observed no meaningful differences in PTAs for weekly vs. daily dosing given with a load. Also, increasing the total weekly dose over 2,000 mg seems to offer minimal additional benefit (Figure 1A–D). Trough-level accumulation is expected as total weekly doses increase, showing a median (IQR) of 62.6 (73.1,85.2) [101.8 (89.9,117.4)] mg/L and 106.5 (91.63,123.6) [135.3 (118.3,156.0)] mg/L at 42 days for the 1,000 mg and 1,500 mg weekly [in equal daily fractions] doses, respectively.

Conclusion. Our design suggests that these DAL dosing regimens in humans are likely to provide reasonable rates of sterilization when treating endocarditis caused by SA isolates, and administration of near 2,000 mg weekly doses may be considered to improve upon sterilizing effect, but at the cost of accumulating DAL levels. Efficacy and safety of new regimens should be confirmed in well-controlled clinical trials.

Dalbavancin Probability of Target Attainment in SA Endocarditis



Disclosures. **All authors:** No reported disclosures.

1564. Target Attainment of Empiric Vancomycin Therapy to Achieve Safe and Effective Exposure When it Matters Most: How Much of the Drug Do We Really Need in the First 48 Hours?
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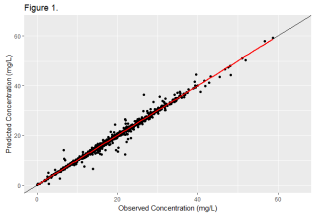
Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

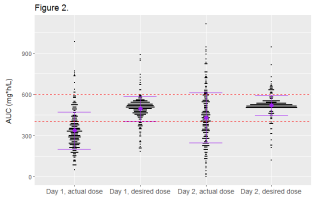
Background. Empiric dosing of vancomycin (VAN) to reach targets is a daunting task due to the large variability observed in the pharmacokinetics of this agent. With the change to AUC driven dosing on the horizon, the goal of this study was to establish empiric dosing requirements of vancomycin that effectively achieve the desired AUC of 400 to 600 mg hours/L targets in the first 48 hours of therapy.

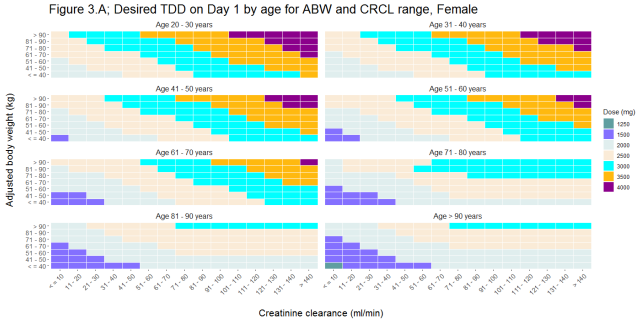
Methods. VAN TDM data were used in this analysis. A two-compartment model was fitted with Bayesian routines to establish the AUCs. Then, the AUC achieved was used to identify the desired total daily dose (TDD, capped at 4,500 mg) needed to attain an AUC in the target range for days 1 and 2, per patient. Next, multivariable regression was undertaken to predict this desired dose with frequently calculated weight and renal function indices. Last, model validation in a test data set based on calculated ME, RMSE and their 95% CI took place, and then the best model was used to simulate TDDs at 24 h intervals. To evaluate the agreement between the 2 pharmacists selecting the final TDDs by screening the simulated regimens, a weighted Kappa was calculated.

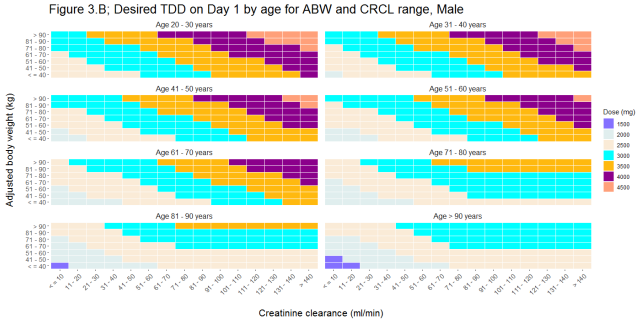
Results. 1450 concentrations from 268 patients (60.9% male) with mean (IQR) age of 62.8 (52.7, 75) years, weight of 79.1 (63.2, 90.9) kg and CrCl of 76.7 (36.8, 110.6) mL/minute were analyzed. Fit of the model to data was excellent with R^2 = 0.98 (Figure 1). AUC attainment with actual dose vs. the AUCs based on the desired dose was poor (Figure 2). Final regression model [ME (95% CI) 31.58 (−160.38, 217.34) mgs; RMSE (95% CI) 761.98 (628.19, 895.93) mgs] identified adjusted body weight (ABW) (P = 0.02), CrCl (P < 0.001), age (P = 0.05) and sex (P = 0.01) on day 1, vs. CrCl (P < 0.001), age (P = 0.02) and sex (P = 0.002) on day 2 as predictors of TDD. Kappas showed near perfect agreement for day 1 (0.992, P < 0.01) and day 2 (0.883, P < 0.01) between the raters resulting in the selection of the final dosing regimens (Figures 3 and 4).

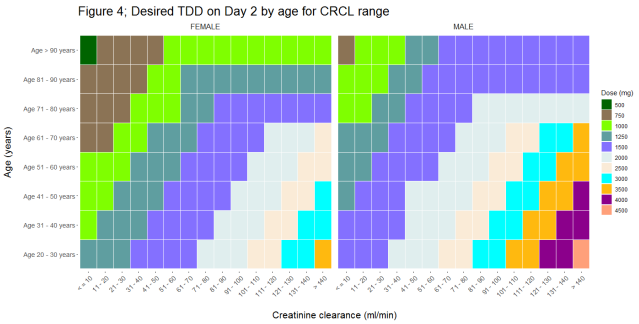
Conclusion. Our model accurately identified the 4 major variables most likely to explain VAN variability in predicting AUC in the first 48 hours. These detailed dosing recommendations—strengthened by rigorous external validation and near perfect between rater agreements—allow for the design of safe and effective AUC driven empiric dosing regimens.











Disclosures. **All authors:** No reported disclosures.

1565. Characterization of Tebipenem (SPR859) Pharmacokinetics–Pharmacodynamics (PK-PD) for Efficacy Against Enterobacteriaceae in a One-Compartment *In Vitro* Infection Model

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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

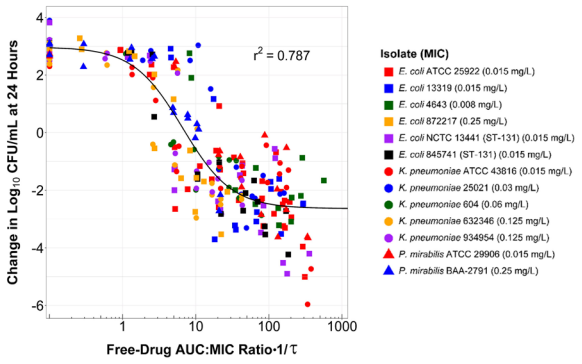
Background. SPR859 (tebipenem) is the active form of the orally bioavailable prodrug SPR994. Tebipenem is an oral carbapenem with a broad-spectrum activity against Gram-positive and -negative bacteria. SPR994 is being developed as an oral option for the treatment of complicated urinary tract infections (cUTI). The goal of these studies was to characterize the PK-PD of tebipenem against a diverse panel of Enterobacteriaceae.

Methods. 24-hour dose-fractionation and dose-ranging studies were carried out utilizing the one-compartment *in vitro* infection model. Bacteria (1×10^6 CFU/mL) were exposed to tebipenem concentrations that mimicked human healthy volunteer free-drug plasma (f) concentration–time profiles following oral drug administration. For the dose-fractionation studies, 7 total daily dose levels (fAUC range, 0.11 to 19.0 mg hours/L) were fractionated in equal divided doses administered every 4, 8 or 12 hours (q4h, q8h and q12h, respectively). A single challenge isolate, *E. coli* ATCC 25922 (MIC = 0.015 mg/L), was evaluated in the dose-fractionation studies. In the dose-ranging studies, 13 Enterobacteriaceae clinical isolates (MIC values from 0.008 to 0.25 mg/L) were exposed to doses ranging from 4.69 to 1200 mg administered q8h (fAUC ranging from 0.14 to 37.2 mg hours/L). Relationships between change in $\log_{10}$ CFU from baseline at 24 h and each of fC_{max}:MIC ratio, f%T>MIC, and fAUC:MIC ratio, with and without adjustment for dosing interval tau for the latter (fAUC:MIC ratio·1/τ), were fit using Hill-type models.

Results. Dose-fractionation study results demonstrated the activity of tebipenem to be time-dependent, with both f%T>MIC and fAUC:MIC ratio·1/τ similarly describing the PK-PD of tebipenem. The relationship between change in $\log_{10}$ CFU from baseline at 24 hours and fAUC:MIC ratio·1/τ, as assessed using pooled data for 13 Enterobacteriaceae isolates evaluated in the dose-ranging studies, described the PK-PD of tebipenem well (Figure 1). The magnitude of fAUC:MIC ratio·1/τ associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU reductions from baseline was 7.23, 13.1, and 32.4, respectively.

Conclusion. These data will be useful to design other pre-clinical studies and support tebipenem dose selection for clinical studies in patients with cUTI.

Figure 1. Relationship between the change in $\log_{10}$ CFU/mL from baseline at 24 hours and tebipenem free-drug AUC:MIC ratio·1/τ based on data for 13 Enterobacteriaceae isolates evaluated in the dose-ranging studies



Disclosures. **All authors:** No reported disclosures.