1555. Risk of Developing Acute Kidney Injury in Patients Receiving Piperacillin–Tazobactam and Vancomycin Compared with Those on Piperacillin–Tazobactam and Telavancin

Joseph Reilly, BS, PharmD, BCGP; Ethan Nhan, PharmD;
Rebecca Erb, BS, PharmD, MTM-C; Cristen A. Whittaker, PharmD;
Manish Trivedi, MD; AtlantiCare Regional Medical Center, Egg Harbor City, New Jersey

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

Background. The combination of piperacillin–tazobactam (PIP-TAZO) and vancomycin is associated with an increased frequency of acute kidney injury (AKI) in patients when compared with either agent alone. Like vancomycin, telavancin is also used for gram-positive infections and has been reported to cause AKI, but there is a paucity of data regarding the development of AKI with the combination of PIP-TAZO and telavancin. The purpose of this study was to compare the incidence of AKI in patients receiving PIP-TAZO with concomitant vancomycin or telavancin.

Methods. This retrospective cohort study included patients admitted between November 2016 and March 2019 who received at least 2 days of either vancomycin or telavancin in combination with PIP-TAZO. Patients were excluded if they had a baseline calculated creatinine clearance of less than 20 milliliters per minute or were receiving renal replacement therapy. Any cases of AKI were defined as a serum creatinine increase of 0.3 milligrams per deciliter (mg/dL) or an increase in creatinine of 1.5 times baseline when observed within 7 days of the studied antibiotic combinations. Statistical analysis was performed to compare baseline characteristics and the development of AKI between the two groups.

Results. Ninety-four patients with an average age of 55 years met the inclusion criteria. Forty-seven patients were included in both treatment arms. There were no statistically significant differences observed between study group baseline characteristics. All patients received PIP-TAZO 3.375 grams every 8 hours as a 4-hour infusion and the average telavancin dose was 7.5 mg/kg. Seventeen of 94 (18%) patients developed AKI, 8(17%) in the vancomycin and PIP-TAZO group and 9 (19%) in the telavancin and PIP-TAZO group ($P = 1.0$). No patients required dialysis.

Conclusion. The development of AKI appears to be similar when comparing vancomycin and PIP-TAZO to telavancin and PIP-TAZO in our population. It is noteworthy that PIP-TAZO was given as an extended infusion and telavancin dosing was lower than the manufacturer recommendations in this evaluation. Additional studies are warranted to further examine the occurrence of AKI with these antibiotic combinations.

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

1556. Assessment of Translational *In Vitro* and Animal Pharmacokinetic–Pharmacodynamic Data Used to Support Drug Development of Recent Tetracycline Derivatives

Jason Moore, PharmD; Sonia Pahwa, PhD; Zhixia Yan Danielsen, PhD;
Philip Colangelo, PharmD, PhD; US FDA, Silver Spring, Maryland

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

Background. Nonclinical (animal and *in vitro*) models are commonly used during the development of antibacterial drugs. Pharmacokinetic (PK) and pharmacodynamic (PD) data obtained from these nonclinical models are used to generate a PK-PD target, which can then be bridged to humans in a probability of PK-PD target attainment (PTA) analysis to support selection of the dose regimen for phase 3 trials and in vitro susceptibility testing criteria (breakpoints) to guide clinical usage.

Methods. Two recently approved tetracycline antibacterial drugs, eravacycline (ERV) and omadacycline (OMD), were evaluated. PK-PD data from nonclinical models and clinical microbiological response were collected from each of the respective clinical pharmacology reviews and assessments published by FDA and EMA, respectively. The highest MICs (minimum inhibitory concentrations) reflecting 80% success in the ability of the drug to inhibit growth in the target bacteria were identified from clinical and nonclinical data and termed the MIC cutoff. The nonclinical MIC cutoff was obtained from the PTA analysis using the PK-PD targets from animal studies. The clinical MIC cutoff was obtained from microbiological response (microbiological intent-to-treat population) data from clinical trial experience. The ratios of the clinical and nonclinical MIC cutoffs were calculated and used to evaluate potential discrepancies between the animal model prediction and clinical trial experience.

Results. The drug development programs for ERV and OMD included murine infection models and in vitro models to characterize PK-PD. The clinical to nonclinical MIC cutoff ratios ranged from 4 to 32. Higher values of the MIC cutoff signify that the drug can treat larger proportions of the bacterial population; therefore, high clinical to nonclinical MIC cutoff ratios signify that the drugs had more activity in reducing the bacterial population in clinical than in nonclinical studies.

Conclusion. Thus, the nonclinical models for ERV and OMD under-predicted microbiological response and breakpoints. While nonclinical models are generally useful, more characterization of translational factors may be needed to allow nonclinical models to be more predictive of clinical trial outcomes.

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

1557. Population Pharmacokinetics of Suvratoxumab (MEDI4893), an Extended Half-life *Staphylococcus aureus* Alpha Toxin-Neutralizing Human Monoclonal Antibody, in Healthy Adults and Patients on Mechanical Ventilation in Intensive Care Units

Vadryn Pierre, PharmD[1]; Bruno Francois, Physician[2];
Martha Hernandez-Illas, MD[3]; Miguel Sánchez Garcia, MD, PhD[4];
Yuling Wu, PhD[5]; Philippe Eggimann, MD[6]; Pierre-Francois Laterre, MD[7];
Vincent Huberlant, MD[8]; Lucia Viña, MD[9]; Thierry Boulain, MD[10];
Alexey Ruzin, PhD[11]; Cédric Bretonnière, MD, PhD[12]; Jerome Pugin, MD[13];
José Trenado Álvarez, MD, PhD[14]; Terramika Bellamy, MS[15];
Kathryn Shoemaker, MS[11]; Omar Ali, PhD[11]; Nancy Lee, PhD[11];
Pierre-Francois Dequin, MD PhD[16]; Hasan S. Jafri, MD[11];
Lorin Roskos, PhD[11]; Susan Colbert, RN, BSN; Rajesh Narwal, PhD[11];
Anis Khan, PhD[11]; [1]Astrazeneca, Columbia, Maryland; [2]CHU Dupuytren Limoges, Limoges, Limousin, France; [3]QPS, Miami, Florida; [4]Hospital Clinico San Carlos, Madrid, Madrid, Spain; [5]Biopharma, Gaithersburg, Maryland; [6]University Hospital and Universits of Lausanne - Switzerland, Lausanne, Vaud, Switzerland; [7]St. Luc University Hospital, University of Louvain, Brussels, Brussels, Brussels Hoofdstedelijk Gewest, Belgium; [8]Centre Hospitalier Jolimont-Lobbes, Jolimont-Lobbes, Hainaut, Belgium; [9]Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain; [10]Centre Hospitalier Régional d'Orléans, Orléans, France, Orléans, Centre, France, [11]AstraZeneca, Gaithersburg, Maryland; [12]Institut du Thorax - CHU Nantes, Nantes, Pays de la Loire, France; [13]Hôpitaux Universitaire de Genève, Geneva, Geneve, Switzerland; [14]Hospital Universitari Mutua Terrassa, Terrassa, Catalonia, Spain, [15]Director, Gaithersburg, Maryland; [16]University of Tours, France, Tours, Centre, France

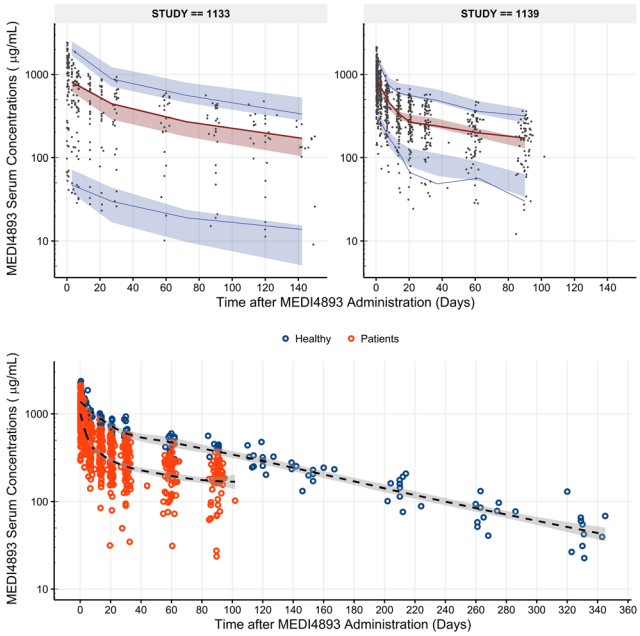
Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

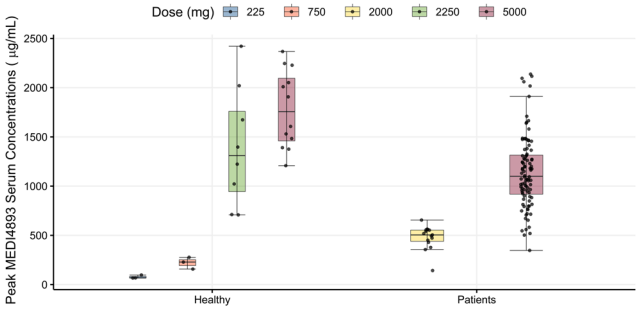
Background. Suvratoxumab (suvra), an extended half-life (~80 days), *Staphylococcus aureus* (SA) alpha toxin-neutralizing IgG monoclonal antibody, is under investigation for prevention of SA pneumonia in patients on mechanical ventilation (MV). We characterized the serum PK of suvra using population pharmacokinetics (popPK) in both healthy volunteers and MV patients and quantified the proportion of patients reaching the serum target of 211 µg/mL at 30 days post-dose.

Methods. The popPK analysis included 1,368 serum samples from two early phase studies (NCT02296320; EudraCT 2014-001097-34): (1) Phase 1 study in 26 healthy adults receiving single IV suvra doses ranging from 0.225g to 5g, with PK sampled up to 360 days; and (2) Phase 2 study in MV patients with PCR-confirmed SA colonization of lower respiratory tract receiving one suvra IV dose of 2g ($n = 15$) or 5g ($n = 96$), with PK sampled up to 100 days.

Results. A two-compartment linear model with weight-based scaling of the PK parameters adequately described the serum PK data (Figure 1). MV status, number of days on MV, and age impacted the PK of suvra. A moderate between-subject variability (<45% CV) was estimated for key PK parameters. An estimated two-fold increase in MV patients' volume of distribution parameters compared with healthy volunteers explained the observed C_{max} differences between the two groups (1145±369 µg/mL vs. 1783±396 µg/mL) (Figures 2 and 3). Although age, MV status and days on MV post-dose appeared to be associated with higher systemic clearance (CL) in the model, this estimate could be biased due to limited PK data available for only one half-life (~90 days) of the drug in MV patients (Figure 2). More patients achieved suvra levels above the PK target following the 5 g (73.5%; 50/68) vs. 2 g dose (7.6%; 1/13) at 30 days post-dose.

Conclusion. MV status, post-dose duration on MV, body weight, and age were identified as statistically significant covariates influencing the PK of suvra. Serum PK and popPK analyses support the 5g dose for future studies with suvra in MV patients.





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

1558. A Population Pharmacokinetic Model for Posaconazole Intravenous Solution and Oral Powder for Suspension Formulations in Pediatric Patients With Neutropenia

Gregory A. Winchell, PhD[1]; Rik de Greef, MSc[1]; Rebecca E. Wrishko, PhD[2]; Eric Mangin, MS[2]; Hetty Waskin, MD/MPH[3]; Christopher Bruno, MD[2]; [1]Certara Netherlands B.V., Oss, Netherlands, Kenilworth, New Jersey; [2]Merck & Co., Inc., Kenilworth, New Jersey; [3]Merck Research Laboratories, Merck & Co., Inc., Kenilworth, New Jersey

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

Background. Posaconazole is approved in adults for prophylaxis and treatment of invasive fungal disease. Two formulations that offer weight-based dosing—intravenous (IV) and oral powder for suspension (PFS)—are being evaluated in children. A population pharmacokinetic (popPK) approach was used to characterize and predict the PK exposure of posaconazole PFS and IV formulations in children to identify dosages associated with achieving a target PK of 1200 ng/mL as the mean C_{avg} and individual C_{avg} ≥500 ng/mL and <2500 ng/mL in ~90% of patients.

Methods. A popPK model was developed through nonlinear mixed-effects modeling using data obtained from a trial in children with neutropenia (ClinicalTrials.gov, NCT02452034; Merck protocol, MK-5592-097). Three dose cohorts (3.5, 4.5, and 6 mg/kg/day [≤300 mg/day]) were studied in two age groups (2–<7 years and 7–17 years). Posaconazole IV was administered twice on day 1 then once daily through at least day 10, followed by PFS once daily through day 28 at clinician discretion. A compartmental model, including both formulations, was fit to the data. Model selection was based on the Log-Likelihood Criterion, goodness-of-fit plots, and scientific plausibility. Significance of the covariates was assessed in a stepwise forward inclusion/backward procedure. An additional assessment characterized the impact of different food covariates on bioavailability.

Results. An open one-compartmental PK model with first-order absorption and estimated bioavailability, as well as allometrically scaled effects of body weight on clearance and volume, adequately described the PK of posaconazole IV and PFS formulations. Model predictions are shown in the Table. Effects of the different food covariates were not statistically significant. Simulations indicated that for the 6-mg/kg/d dose, model-predicted C_{avg} generally met PK targets. Model-predicted C_{avg} was ≥500 ng/mL in >90% of subjects in all cohorts. The 1200-ng/mL target geometric mean C_{avg} was achieved for all but the 2–<7 years cohort receiving the PFS formulation.

Conclusion. This popPK-based analysis demonstrated that the 6-mg/kg/d dose of IV or PFS posaconazole formulation (≤300 mg/days) is appropriate for children (2–17 years) and that PFS can be administered without regard to food.

Table. Model-predicted geometric mean C_{avg}, percentage of patients in prespecified posaconazole steady state C_{avg} target range, and percentage of patients achieving C_{min} ≥500 ng/mL after IV and oral PFS administration of posaconazole 4.5, 6.0, or 7.5 mg/kg/d (to ≤300 mg/d) in children

Dose Cohort, mg/kg/d	Age Group, y	Formulation	Model-Predicted Percentage of Patients With C_{avg}			Model-Predicted Geometric Mean C_{avg}, ng/mL (%GCV)	Model-Predicted Percentage of Patients With C_{min} ≥500 ng/mL, %
			<500 ng/mL, %	500-2500 ng/mL, %	>2500 ng/mL, %		
4.5	2 to <7	IV	2.8	95.6	1.6	1045 (40)	55
		PFS	17.2	82.1	0.7	796 (51)	52
	7 to 17	IV	0.8	93.4	5.8	1361 (42)	79
		PFS	7.6	89.9	2.5	1042 (52)	76
6.0	2 to <7	IV	0.2	94.4	5.4	1365 (39)	70
		PFS	6.8	91.2	2.0	1050 (50)	69
	7 to 17	IV	0.1	82.2	17.7	1748 (41)	90
		PFS	3.1	89.1	7.8	1332 (51)	86
7.5	2 to <7	IV	0	83.2	16.8	1714 (40)	79
		PFS	2.9	89.3	7.8	1321 (51)	80
	7 to 17	IV	0	70.2	29.8	2001 (42)	94
		PFS	1.9	82.1	16.0	1547 (53)	90

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

1559. Ertapenem Plus Ceftriaxone or Ceftaroline Dual B-Lactam Combination for *Enterococcus faecalis*

Jaclyn A. Cusumano, PharmD[1]; Kathryn E. Daffinee, BS[2]; Kerry LaPlante, PharmD[2]; [1]Providence VA Medical Center / University of Rhode Island, Warwick, Rhode Island; [2]Rhode Island Infectious Diseases Research Program, Providence, Rhode Island

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

Background. Ampicillin-ceftriaxone β-lactam therapy has become the standard of care for treating serious *Enterococcus faecalis* infections. Alternative regimens are of interest due to ceftriaxone's association with *C. difficile* infections and VRE colonization, and ampicillin's instability and inconvenient dosing schedule.

Methods. *E. faecalis* wild-type strain JH2-2 was utilized in a 48-hour in vitro pharmacodynamic model with a starting inoculum of 10^6 colony-forming units (CFU)/mL. Models were performed in duplicate to triplicate. Simulated doses of ertapenem 1g every 24 hours (fCmax 12.2 µg/mL; half-life 4 hours; MIC 4 µg/mL), ceftriaxone 2 g every 12 hours (fCmax 28.5 µg/mL; half-life 6.5 hours; MIC 512 µg/mL), and ceftaroline 600 mg every 8 hours (fCmax 27.1 µg/mL; half-life 2.7 hours; MIC 2 µg/mL) were tested. Ertapenem was also combined with ceftriaxone or ceftaroline. Bacterial counts were obtained at 0, 4, 8, 24, 32, and 48 hours. Bactericidal activity was defined as ≥ 3-log10 CFU/mL reduction from the initial inoculum. MICs were assessed at 0, 24, and 48 hours using E-tests in accordance with CLSI.

Results. Ertapenem plus ceftriaxone, and ertapenem plus ceftaroline demonstrated bactericidal activity at 24 hours, but bacterial regrowth was observed at 48 hours (Table 1). An ertapenem MIC increase was only noted in one set of the ertapenem plus ceftriaxone models to 16mcg/mL at 48 hours, from 4mcg/mL at 0 hours. All other models did not have an increase in MIC.

Conclusion. Bactericidal activity of ertapenem-based dual β-lactam combinations may prove to be an alternative treatment for severe *E. faecalis* infections. Mechanistic understanding of penicillin-binding protein (PBP) saturation and optimization of antimicrobial pharmacodynamics must be explored.

Table 1. Average Bacterial log_{10} CFU/mL ± Standard Deviation (SD)		
Antibiotics	**24 Hours**	**48 Hours**
Ertapenem Alone	7.35 ± 0.46	7.21 ± 0.6
Ceftriaxone Alone	6.67 ± 0.18	7.46 ± 0.03
Ceftaroline Alone	4.65 ± 0.67	5.97 ± 0.18
Ertapenem + Ceftriaxone	1.79 ± 0.91*	4.72 ± 0.52
Ertapenem + Ceftaroline	2.29 ± 1.0*	5.05 ± 0.25

*bactericidal activity

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

1560. Pharmacokinetics–Pharmacodynamics (PK-PD) of Gepotidacin (GEP) Against *Escherichia coli* in Murine Pyelonephritis and Thigh Infection Models

Aline Barth, MSc, PhD; Cindy l. Mininger, BS; Thomas Lewandowski, BS; Mohammad Hossain, PhD; Stephen Rittenhouse, PhD; Jennifer Hoover, BS; GlaxoSmithKline, Collegeville, Pennsylvania

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

Background. GEP, a first in class novel triazaacenaphthylene bacterial topoisomerase inhibitor, inhibits bacterial replication and has in vitro activity against key pathogens implicated in a range of infections, including drug-resistant strains of *E. coli* associated with acute cystitis.

Methods. PK and PD studies were conducted in murine (male CD-1 mice) thigh and kidney infections. The administered doses ranged from 1 to 200 mg/kg SC every 6 hours starting 1-hour post-infection. Infected tissues were evaluated for bacterial burden at 24-h post-infection (baseline controls at 1-hour post-infection). Plasma and tissue samples (kidney or thigh homogenates) were collected at 15, 30, 60, 120, 240 and 360 minutes. A population PK (PopPK) model was built in NONMEM using plasma exposures. Efficacy was determined against *E. coli* ALL, 997577, ATCC25922, IR5 and NCTC13441 (MICs of 1 to 4 µg/mL) in thigh-infected neutropenic (I-) mice and against *E. coli* ALL in kidney-infected immunocompetent (I+) and I- mice. The PopPK model was used to determine GEP exposures associated with efficacy. PK-PD analyses were conducted using Phoenix WinNonLin 6.3 (Pharsight). The change in log_{10} colony-forming units (CFU) from baseline were correlated with free drug (f) AUC:MIC using an inhibitory model from the Phoenix library, and model parameter values for each isolate were used to calculate the plasma fAUC:MIC associated with stasis, 1- or 2-log_{10} reductions in CFU.

Results. Plasma PK data were best fit by a 1-compartment IV model with first-order elimination and were similar in I+ vs. I- and thigh- vs. kidney-infected mice. The AUC_{0-6} of GEP in kidney was approximately 4- to 5-fold higher than in plasma while the AUC_{0-6} in thigh was approximately half of plasma. In the I- thigh model, median plasma fAUC:MIC ratios for stasis, 1- or 2-log_{10} reductions in CFU were 11, 16, and 25 (ranges 3–17, 4–25 and 7–40), respectively. Efficacy vs. *E. coli* ALL was similar in I- mice infected in thigh or kidney. In I+ mice, the PK-PD target was reduced by half.

Conclusion. Median plasma fAUC:MIC targets ranged from 11 to 25. Higher drug levels in kidney vs. plasma or thigh did not translate into improved efficacy in pyelonephritis vs. thigh-infection models.

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

1561. Omadacycline Pharmacokinetics: Influence of Mortality Risk Score Among Patients with Community-Acquired Bacterial Pneumonia

Elizabeth A. Lakota, PharmD, MS[1]; Lawrence Friedrich, PharmD[2]; Judith N. Steenbergen, PhD[2]; Paul C. McGovern, MD[2]; Evan Tzanis, BA[2];