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Session: P-59. PK/PD studies

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 pharmocophores in this patient population can lead to biased parameter estimates. In order to prevent potential bias an agnostic nonparametric adaptive grid approach to describe celfluzalone/tazobactam (C/T) PopPK profiles in patients with partial- and full-thickness burns was employed.

Methods. A human clinical PK study in burn patients was conducted using the standard approved dose of C/T (2 grams/1 gram). A single intravenous dose was administered over 60 minutes. Whole blood was obtained pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours following the start of infusion. LC-MS/MS bioanalytical methods were developed, validated and employed to determine C/T concentrations in human plasma. PopPK were modeled using PMetrics package for R. One- two- and three-compartment models were examined and compared. The influence of several parameters, including %body surface area burns, creatinine clearance (CrCL), weight, albumin and age were tested.

Results. The bioanalytical method for determination of C/T in human plasma met all recommended criteria of the LC-MS/MS. Five males and one female (ages 24 to 66 years), contributed 148 plasma PK samples. The female had 35% partial-thickness burns. The males had full-thickness burns ranging from 27 to 66%. The median CrCL was 104 mL/min (range 73-148 mL/min). Two-compartment model with absorption (Ka) from compartment 1 to 2 and elimination from compartment 2 (Ke), with nonlinear interactions between C/T elimination and CrCl best described the data. Figure A showed that bias was minimal. Importantly, both drugs exhibited marked variability for both volume and elimination (Table), since volume was bimodally distributed (Figure B).

A) Observation-versus-Prediction; B) Estimated Ke, V and Ka population parameter densities

Summary of Pharmacokinetic parameters

| Parameter | Mean | SD | %CV | Median | %Shrinkage |
|-----------|------|----|-----|--------|------------|
| Cefozoxane | | | | | |
| Ke | 4.232 | 8.760 | 206.994 | 0.275 | 0.001 |
| V | 157.610 | 275.586 | 174.853 | 28.956 | 0.006 |
| Ka | 4.785 | 1.283 | 268.070 | 5.355 | 0.003 |
| Tazobactam | | | | | |
| Ke | 0.649 | 0.253 | 36.829 | 0.567 | 6.022 |
| V | 206.158 | 356.308 | 172.831 | 36.555 | 0.007 |
| Ka | 20.493 | 15.279 | 74.631 | 15.973 | 1.531 |

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

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1320. Pharmacokinetics of Isavuconazole Administered as Isavuconazonium Sulfate Intravenous Solution via Nasogastric Tube or Orally in Healthy Volunteers Amit Desai, PhD1; Melanie Helmick, BA, Clinical Research; Nakyo Heo, PharmD, MS1; Selina Moy, BS1; Stephen Stanhope, PhD1; Ronald Goldwater, MD, MDCM2; Nancy Martin, MD, PharmD1; Astellas Pharma Global Development, Northbrook, IL, Northbrook, Illinois; 2Parexel International Corporation, Baltimore, Maryland

Session: P-59. PK/PD studies

Background. Nasogastric (NG) tube feeding is most common in the intensive care unit and is also used for cancer patients who are unable to eat (e.g. patients with mucositis) or do not want to eat due to severe nausea. For such critically ill patients with invasive fungal infections, administration of isavuconazonium sulfate (ISAVUSULF) via NG tube can be an alternate route of drug administration.

Methods. This was a randomized, open-label, 2-period, 2-sequence single dose crossover study in healthy male and female subjects. Each subject participated in 2 treatment periods separated by a washout of at least 30 days between investigational product administrations in each period. Subjects were administered a single dose of 372 mg ISAVUSULF intravenous (IV) solution via NG tube (test formulation) or 372 mg ISAVUSULF capsules for oral (PO) administration (i.e., PO capsules administered to subjects without NG tube) (reference formulation) under fasting conditions on day 1 of each period. Pharmacokinetic (PK) samples were collected predose on day of dose administration and at multiple time points postdose through day 21. Safety and tolerability assessments were conducted in each period.

Results. Eighteen subjects were randomized in this study and 13 provided concentrations in both sequences that were PK evaluable. The analysis of variance estimate (Table 1) of the study population suggests that the isavuconazole IV NG tube administration geometric least-square (LS) mean values of the observed maximum concentration (Cmax), area under the plasma concentration-time curve (AUC) to the last measurable concentration (AUC0-τ), AUC to time infinity (AUC∞) and AUC from start of dosing to 72 hours (AUC0-inf) were 105.3%, 97.6%, 99.3% and 97.8%, respectively, of the corresponding oral administration values. The geometric LS mean ratio and 90% Confidence Intervals for the Cmax, AUC0-τ, AUC∞ and AUC0-inf are completely contained within the prespecified limits of 80% to 125%. There were no deaths or serious adverse events that led to withdrawal of treatment during the conduct of the study.

Table 1: Statistical Assessment of Bioequivalence of Isavuconazonium Sulfate IV Solution versus NG Tube (Test Formulation) Compared to Isavuconazonium Sulfate Oral Capsules (Reference Formulation)

| Parameter | Isavuconazonium Sulfate IV Solution (Test Formulation) | Isavuconazonium Sulfate Oral Capsules (Reference) | Geometric LS Mean Ratio (%) | 90% CI of Ratio |
|-----------|------------------------------------------------------|-------------------------------------------------|---------------------------|----------------|
| n | Geometric LS Mean | n | Geometric LS Mean | |
| Cmax | mg/L | 12 | 90.30 | 12 | 91.00 | 99.3 | (92.70, 106.29) |
| AUC0-τ | mg·hr/L | 13 | 81.14 | 13 | 83.40 | 97.6 | (92.37, 105.13) |
| AUC∞ | mg·hr/L | 13 | 84.60 | 13 | 84.40 | 97.6 | (92.67, 100.24) |
| AUC0-inf | mg·hr/L | 13 | 2256 | 13 | 2120 | 106.3 | (92.25, 124.33) |

*90% confidence limits are transformed back to raw scale and values are expressed as percentages.

Conclusion. The study met its primary endpoint of bioequivalence between the two routes of administration in this population. Both routes of administration are well tolerated.

References: 1. Pike, S., and B. Bohmer. 1998. Options for artificial nutrition of cancer patients. Strahlenther. Onkol. 174:52-55

Disclosures. Amit Desai, PhD, Astellas Pharma Inc. (Employee, Other Financial or Material Support, This study was initiated and sponsored by Astellas Pharma Global Development Inc) Melanie Helmick, BA, Clinical Research, Astellas Pharma Inc. (Employee, Other Financial or Material Support, This study was initiated and sponsored by Astellas Pharma Global Development Inc) Nancy Martin, MD, PharmD, MS, Astellas Pharma Inc. (Employee, Other Financial or Material Support, This study was initiated and sponsored by Astellas Pharma Global Development Inc) Nakyo Heo, PharmD, MS, Astellas Pharma Inc. (Employee, Other Financial or Material Support, This study was initiated and sponsored by Astellas Pharma Global Development Inc) Stephen Stanhope, PhD, Astellas Pharma Inc. (Employee, Other Financial or Material Support, This study was initiated and sponsored by Astellas Pharma Global Development Inc) Ronald Goldwater, MDCM, Astellas Pharma Inc. (Other Financial or Material Support, This study was initiated and sponsored by Astellas Pharma Global Development Inc) Parexel International received fees for research support from Astellas Pharma Global Development Inc.) Randal Goldwater, MDCM, Parexel International Inc. (Employee, Other Financial or Material Support, This study was initiated and sponsored by Astellas Pharma Global Development Inc)

1321. Population Pharmacokinetic (PK) and Pharmacokinetic/Pharmacodynamic (PK/PD) Target Attainment Analyses for Dalbavancin in Pediatric Patients Timothy J. Carothers, ScD1; H. Maxine Llagasau, PhD2; Lars Lindholm, PhD2; Todd Riccobene, PhD3; AbbVie, Madison, New Jersey; 3pharma LLC, Cary, North Carolina; 2Allergan plc, Madison, NJ

Session: P-59. PK/PD studies

Background. Dalbavancin is a lipoglycopeptide approved for treating adults with acute bacterial skin and skin structure infections (ABSSSI). It has a terminal half-life of >14 days, which allows for administration as a single-dose regimen. Pediatric studies for dalbavancin include three phase 1 studies and a phase 3 study in patients from birth to 17 years with ABSSSI or neonatal sepsis.

Methods. A population PK model was developed using 1124 concentrations from 211 pediatric patients. Allometric scaling of clearance, and volume parameters was included with exponents fixed at 0.75 and 1, respectively. Based on exploratory analysis and prior knowledge, serum albumin was included as a covariate on all PK parameters, and creatinine clearance or estimated glomerular filtration rate (eGFR) was included as a covariate on clearance. eGFR for patients < 2 years accounted for renal maturation. Additional covariates were assessed by stepwise covariate modeling (SCM). The final model was qualified by visual predictive checks (VPCs) and bootstrapping and

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was used to simulate 1000 PK profiles for various pediatric age groups, ranging from preterm neonates to adolescents. PK/PD target attainment (PTA) was calculated for targets associated with stasis, 1-log kill, and 2-log kill of *Staphylococcus aureus* in the murine thigh infection model.

**Results.** Dalbavancin PK was well-characterized by a 3-compartment model. SCM did not find any significant covariates besides albumin, weight, and renal function. VPCs demonstrated that the final model has good predictive performance across the full age range. Simulations showed that single-dose regimens of 22.5 mg/kg for patients < 6 years and 18 mg/kg for patients 6 to < 18 years resulted in PTA ≥94% for MICs up to 2 mg/L for the stasis target and up to 0.5 mg/L for the 2-log kill target. PTA for pediatric patients was similar to adults, and exposures (AUCs) were contained within the range for adults administered 1500 mg.

**Conclusion.** Dalbavancin PK in pediatric patients was well-characterized by a 3-compartment model with allometric scaling of clearance and volume and with albumin and renal function included as covariates. Simulations with the final model demonstrate adequate PTA across the entire age range for the regimens used in the phase 3 pediatric study.

**Disclosures.** Timothy J. Carrothers, ScD, AbbVie (Employee) Maxime Lagraauw, PhD, qPharma (Employee) Lars Lindbom, PhD, qPharma (Employee) Todd Riccobene, PhD, AbbVie (Employee)

### Table 1.

| Parameter | Value |
|-----------|-------|
| Age (years) | 40-70 |
| BMI (kg/m²) | 18-30 |
| QTc (ms) | 450-800 |
| Body weight (kg) | 30-120 |
| Drug administration history and ECG recording data | collected from the electronic medical record database |

**Results.** Data from 2180 patients were used with baseline characteristics shown in Table 1. Observed vs. predicted plots based on the training (Figure 1.A) and validation data set (Figure 1.B) showed excellent fit. The model developed accurately identified the impact of commonly used anti-infectives on the QT interval in hospitalized patients during the COVID-19 era.

**Methods.** Demographic information, medical history, laboratory data, medication administration history and ECG recording data was collected from the electronic records of adult patients admitted to two urban hospitals. A mixed effects approach that incorporated fixed and random effects with between occasion variability was estimated for the parameters with a Bayesian approach using the STAN software.

**Results.** Data from 2180 patients were used with baseline characteristics shown in Table 1. Observed vs. predicted plots based on the training (Figure 1.A) and validation data set (Figure 1.B) showed excellent fit. The parameters for QTc, age, gender, and circadian rhythm were identified within the range previously described (Table 2). Similarly, the model correctly identified the impact of acute or chronic diseases on the QT interval. Model coefficient estimates [mean (95% CI)] of 0.007 (0.006, 0.15) and 0.0045 (0.003, 0.011) msec/mg cumulative dose, respectively, suggest that patients treated with conventional regimens of fluconazole and levofloxacin are most likely to present with a QT interval increase > 5 msec, the cutoff threshold of regulatory concern.

**Conclusion.** Dalbavancin PK in pediatric patients was well-characterized by a 3-compartment model with allometric scaling of clearance and volume and with albumin and renal function included as covariates. Simulations with the final model demonstrate adequate PTA across the entire age range for the regimens used in the phase 3 pediatric study.

**Disclosures.** Timothy J. Carrothers, ScD, AbbVie (Employee) Maxime Lagraauw, PhD, qPharma (Employee) Lars Lindbom, PhD, qPharma (Employee) Todd Riccobene, PhD, AbbVie (Employee)

### Table 2.

| Parameter | Value |
|-----------|-------|
| Population Mean (95% CI) | 0.007 (0.006, 0.15) |
| SCM | 0.0045 (0.003, 0.011) |

**Results.** Data from 2180 patients were used with baseline characteristics shown in Table 1. Observed vs. predicted plots based on the training (Figure 1.A) and validation data set (Figure 1.B) showed excellent fit. The model developed accurately identified the impact baseline risk factors and concomitant medications have on the QT interval. When adjusted for these confounding variables, estimates of QT interval prolongation show that treatment with fluconazole and levofloxacin pose a considerable risk; while treatment with azithromycin or hydroxychloroquine is of moderate risk for QT interval prolongation.

**Disclosures.** All authors reported disclosures.

**1323. Substantial Doses of Daptomycin and Rifampin Eradicate S. epidermidis Biofilm in an In Vitro Pharmacodynamic (IVPD) Model**

**Session:** P-59. PK/PD studies

**Background.** The concentration of antibiotics at the site of action needed to eradicate biofilm is currently unknown. Studies have previously suggested that bacteria in biofilms are 1000-fold more resistant to antibiotics than free-floating planktonic bacteria. We sought to describe concentrations of daptomycin alone and in combination with rifampin in relation to the pharmacodynamic exposures for biofilm eradication.

**Methods.** We utilized a methicillin-resistant high biofilm-forming *S. epidermidis* strain R66a (ATCC® 35984) over a 48-hour in vitro PD biofilm model. The Centers for Disease Control (CDC) Biofilm Reactor model was used with chromium cobalt materials to simulate an orthopedic device infection. The reactor was inoculated and underwent a 24-hr growth phase and 16-hr conditioning phase to form biofilm on the chrome-embedded surface. VPCs demonstrated that the final model has good predictive performance across the entire age range for the regimens used in the phase 3 pediatric study.

**Conclusion:** The model developed accurately identified the impact baseline risk factors and concomitant medications have on the QT interval. When adjusted for these confounding variables, estimates of QT interval prolongation show that treatment with fluconazole and levofloxacin pose a considerable risk; while treatment with azithromycin or hydroxychloroquine is of moderate risk for QT interval prolongation.

**Disclosures.** All authors reported disclosures.