Pooled nephrotoxicity rates from trough-guided monitoring

Conclusion. The AUC-guided approach appeared to have lower risk of nephrotoxicity which supports the updated American Society of Health-System Pharmacists recommendations. More studies should be performed to evaluate the optimal derivation of AUC and clinical utility of repeated measurements of vancomycin AUC and trough levels.

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

1098. A Phase 1 Safety and Tolerability of Single Ascending Doses of a Novel Engineered Cationic Peptide, PLG0206, in Healthy Subjects

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Session: P-62. PK/PD Studies

Background. PLG0206 is a novel engineered cationic antimicrobial peptide being evaluated for treatment of prosthetic joint infections (PJI). This abstract presents the results from the first in human study to evaluate the safety, tolerability and pharmacokinetic (PK) profile of PLG0206 when administered as an intravenous (IV) infusion.

Methods. 6 cohorts of 8 participants were planned to receive escalating single 1-hour IV infusions of PLG0206 at 0.05, 0.125, 0.25, 0.5, 1, 2 and 3 mg/kg dose or placebo. Participants were randomized to receive either PLG0206 (6 per cohort) or placebo (2 per cohort). At each dose level, there were 2 sentinel participants (1 active, 1 placebo) who were dosed at least 48 hours in advance of the other participants in their group. Serial pharmacokinetic samples were taken prior to infusion and up to 48 post infusion. Safety and tolerability was assessed throughout the study. There was at least a 7-day period after dosing at each of the dose levels before dose escalation.

Results. PLG0206 was safe and well tolerated when administered to healthy volunteers at doses ranging from 0.05 and 1 mg/kg. Therapeutic exposures were achieved at 1 mg/kg. The 2 and 3 mg/kg cohorts were not studied. The incidence of treatment emergent adverse events related to study drug administration was low and most events mild (Grade 1) in severity and was similar between the PLG0206 treatment and placebo groups. There were no SAEs, life-threatening events or deaths throughout the study. IV PLG0206 exhibited linear PK over the dose range of 0.05 to 1.0 mg/kg. The median terminal half-life (t½) ranged from 7.37 to 19.97 hours. $AUC_{0-\infty}$ increased with increasing PLG0206 dose ranging between 1581.41 and 21141.52 ng.hr/mL. Cmax ranged between 256 and 2653 ng/mL. The mean apparent volume of distribution (Vz) increased was between 25.49 and 94.2 L, mean clearance (CL) were similar across all and ranged from 2.42 to 4.18 L/hour.

Conclusion. Following single IV infusion to healthy volunteers, PLG0206 was safe and well tolerated at doses ranging from 0.05 to 1 mg/kg. IV PLG0206 exhibits linear PK over the dose range. These findings support the ongoing development of IV PLG0206 and will inform dosing regimens in future studies to investigate its utility as an antimicrobial agent.

Disclosures. **David Huang, MD, PhD**, **Peptilogics** (Employee) **Despina Dobbins, BS**, **Peptilogics** (Employee) **Parviz Ghahramani, PhD, PharmD, MSc, MBA**, **Peptilogics** (Consultant) **Jonathan Steckbeck, PhD**, **Peptilogics** (Employee)

1099. Evaluation of the Safety and Pharmacokinetics (PK) following Administration of Single and Multiple Doses of Anti-Staphylococcal Lysin, LSVT-1701, in Healthy Adult Subjects

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Session: P-62. PK/PD Studies

Background. LSVT-1701 is an anti-staphylococcal phage lysin being developed for treatment of MRSA infections in combination with SoC antibiotics. The safety and PK of single ascending doses of LSVT-1701 0.1 to 10 mg/kg in healthy adult volunteers were previously described (Jun, et.al, AAC 2017;61:e02629-16). We further evaluated the safety and PK of multiple ascending doses of LSVT-1701 in healthy adult subjects.

Methods. Study ITB-101-1b was a Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study. 8 subjects were randomized 3:1 to active:placebo in each cohort. LSVT-1701 was administered as a 6 mg/kg single dose and twice daily (BID) doses of 1.5, 3.0, and 4.5 mg/kg for 4 days (24h between Doses 1-2, 12h between Doses 2-6). Study drugs were administered as a 1-hour IV infusion. Serial serum samples were collected over 24 hours following the first and last doses for measurement of LSVT-1701 concentrations by a validated ELISA method. PK analysis of LSVT-1701 concentration-time data was done using noncompartmental methods. Safety was assessed by AEs, clinical labs, vital signs, and ECG.

Results. 30/32 (94%) subjects completed the study. No subjects withdrew due to AEs, and there were no severe AEs, no serious AEs, and no deaths. AEs were of mild (97%) to moderate (3%) intensity and were reported by all subjects in the LSVT-1701 6 mg/kg single dose group and 1-3 (17-50%) of subjects receiving 1.5 to 4.5 mg/kg BID or placebo. The most common AEs of headache, chills, rigors, and fever generally lasted for ≤2 days with or without acetaminophen treatment, and no clinically significant changes in blood pressure, heart rate, ECG, or clinical labs (other than transient increases in CRP) were observed. Infusion site reactions (erythema, pain, induration, warmth) were observed with BID administration of LSVT-1701, but not with the single 6 mg/kg dose or placebo. LSVT-1701 exposure increased greater than in proportion to dose and $t_{1/2}$ was concentration-dependent, increasing with higher doses. No accumulation in LSVT-1701 exposure was observed.

Summary of LSVT-1701 PK Parameters

LSVT-1701 Dose (mg/kg) BID [N=6/cohort]	Day	Mean (SD)		
		AUC[a] (µg.h/mL)	Cmax (µg/mL)	t/1/2 (h)
1.5 single dose (N=6)	1	1.14 (0.519)	1.24 (0.509)	0.39 (0.08)
3.0 single dose (N=6)	1	5.70 (1.35)	4.93 (1.08)	0.73 (0.21)
4.5 single dose (N=6)	1	11.8 (1.15)	10.8 (1.53)	1.16 (0.29)
6.0 single dose (N=6)	1	24.8 (7.05)	21.4 (3.91)	3.38 (3.40)
1.5 BID (N=6)	4	1.23 (0.657)	1.30 (0.696)	0.45 (0.16)
3.0 BID (N=6)	4	5.70 (1.34)	5.01 (1.21)	2.02 (0.78)
4.5 BID (N=6)	4	10.3 (1.56)	10.2 (1.43)	3.72 (2.85)

[a]AUC = AUCinf for single doses (Day 1) and AUCτ for multiple dose (Day 4)

Summary of LSVT-1701 PK Parameters

Conclusion. The safety and PK profile of LSVT-1701 is favorable for evaluation in patients with

S. aureus infections, including bacteremia and infective endocarditis, for which new treatments are needed.

Disclosures. **Mary Beth Wire, Pharm#**, **Lysovant** (Consultant) **Soo youn Jun, PhD**, **iNtRON Biotechnology** (Consultant) **In-Jin Jany, PhD**, **iNtRON** (Consultant) **Jun Gi Hwang, PhD**, **Lysovant** (Consultant) **David Huang, MD, PhD**, **Lysovant** (Consultant)

1100. A Prospective Evaluation of Neurotoxicity Among Patients Receiving Dose-Optimized Cefepime or Meropenem With Concomitant Therapeutic Drug Monitoring

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Session: P-62. PK/PD Studies

Background. Cefepime (FEP) induced neurotoxicity (NT) may have serious implications for patients (pts). Retrospective studies have employed variable definitions of NT, finding renal impairment and FEP trough concentrations (Cmin) > 20 mg/L as risk factors. Prospective studies comparing antibiotics have not been performed.

Methods. We conducted a prospective study of pts receiving FEP or meropenem (MEM) with neurologic evaluation and therapeutic drug monitoring (TDM). A NT advisory board (NTAB) was established to develop standardized definitions of possible, probable and definitive NT (Fig 1). Cases of potential NT were adjudicated by the NTAB who were blinded to study treatment. FEP and MEM midpoint and Cmin concentrations were measured at steady-state by validated methods.

Figure 1. Neurotoxicity Definitions

Beta-lactam Neurotoxicity	Onset of Symptoms	Alternative Diagnosis	EEG Findings	Neuroimaging findings	Clinical Improvement
Unlikely	Prior to beta-lactam initiation or after beta-lactam discontinuation	Alternative diagnosis **more likely** to have caused clinical syndrome	EEG normal or changes **consistent** with alternative explanation	Neuroimaging **absent or inconclusive** for etiology of neurotoxicity.	No clinical improvement after discontinuation of beta-lactam
Possible	During beta-lactam therapy	Alternative diagnosis **as likely** to have caused clinical presentation	EEG changes **equally consistent** with beta-lactam neurotoxicity or alternative explanation	Neuroimaging **absent or inconclusive** for etiology of neurotoxicity.	No clinical improvement or unclear clinical improvement after discontinuation of beta-lactam
Probable	≤ 5 days from ≥ 1 of the following: Beta-lactam initiation or Dose increase or Worsening renal function	Alternative diagnosis **less likely** than beta-lactam to have caused symptoms	EEG changes **consistent** with beta-lactam neurotoxicity and alternative explanation **less likely**	Neuroimaging **less likely** to support alternative etiology of neurotoxicity	Clinical improvement after discontinuation of beta-lactam
Definitive	≤ 5 days from ≥ 1 of the following: Beta-lactam initiation or Dose increase or Worsening renal function	Alternative diagnosis **much less** likely to have cause symptoms	EEG changes **consistent** with beta-lactam neurotoxicity **without** alternative explanation **and** improvement in EEG **off** of beta-lactam	Neuroimaging **not supportive** of alternative etiologies for neurotoxicity	Clinical improvement after discontinuation of beta-lactam

Objective Neurotoxicity	Subjective Neurotoxicity	Neurologic Adverse Reactions
Ataxia	Altered mental status	Headache
Encephalopathy	Cognitive disturbances	Dizziness
Myoclonus	Paresthesia	Blurry vision
Seizures	Somnolence	Other
Non-epileptiform EEG changes (See separate chart)	Difficulty awakening from sedation	

Neurotoxicity Advisory Board (NTAB)	
ID Physician	ID Pharmacist
Intensivist	Neuro Intensivist
Epileptologist x2	

Results. 127 patients were included (70 FEP, 57 MEM). Demographics and treatment characteristics were similar between groups (Fig 2); 63% were in the ICU. FEP and MEM Cmin varied from 1.9 – 140.5 and 0.6 – 31.3 mg/L, respectively. Median FEP Cmin and total exposures (AUC) were 23.1 mg/L and 347.6 hr*mg/L, respectively. Corresponding MEM values were 5.9 mg/L and 124.8 hr*mg/L, respectively. Cmin values were inversely correlated with renal function for both FEP and MEM (P< 0.001). Rates of possible, probable, or definitive NT were 10% and 5% for FEP and MEM, respectively (P=0.51; Fig 3). 16% and 3% of pts with FEP Cmin > or < 20 mg/L had NT, respectively (P=0.11; Fig 4). Median MEM Cmin were 12.3 and 5.4 mg/L among pts with and without NT, respectively (P=0.09; Fig 4). Rates of NT did not vary by infusion length or dose. FEP and MEM exposures were similar between patients with (17%) or without (83%) microbiologic recurrence due to the same pathogen. FEP was discontinued in 4 pts due to NT; no pts stopped MEM due to NT.

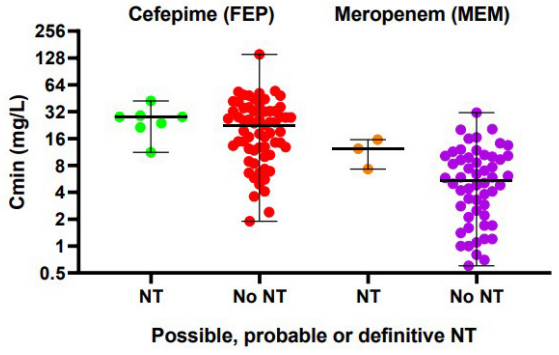
Figure 2. Patient Demographics and Treatment Characteristics

Patient Demographics	Cefepime N= 70 (%)	Meropenem N = 57 (%)
Sex (female)	26 (37.1%)	19 (33.3%)
Median Age (Range)	61 (23-87)	59 (18-85)
ICU Admission	42 (60.0%)	38 (66.6%)
ID Consult	47 (67.1%)	45 (78.9%)
Treatment Indication	Bacteremia: 20 (28.6%) Pneumonia: 28 (40.0%) Empiric: 5 (7.1%) Other: 17 (24.3%)	Bacteremia: 19 (33.3%) Pneumonia: 19 (33.3%) Empiric: 6 (10.5%) Other: 13 (22.8%)
Selected Comorbidities	**Cefepime N= 70 (%)**	**Meropenem N = 57 (%)**
Chronic Kidney Disease	15 (21.4%)	11 (19.3%)
End Stage Renal Disease (dialysis)	4 (5.7%)	3 (5.3%)
Seizure Disorder	5 (7.1%)	5 (8.8%)
Prior Adverse Neurologic Reaction to β-lactam	0 (0.0%)	3 (5.3%)
Stroke Hemorrhagic Ischemic	5 (7.1%) 2 (2.9%) 3 (4.3%)	1 (1.8%) 1 (1.8%) 0 (0.0%)
Alcohol Use Disorder	7 (10.0%)	3 (5.3%)
Treatment Characteristics	**Cefepime N= 70 (%)**	**Meropenem N = 57 (%)**
Median duration of treatment (Range)	8 (3 – 53)	11 (2 – 118)
Median time to PK sampling, hours (Range)	60.1 (24 - 293)	63.6 (13 - 325)
Trough concentration range	1.9 – 140.5	0.6 – 31.3
Median trough concentration CrCl > 60 mL/ min CrCl < 60 mL/ min	 12.7 mg/L 28.1 mg/L	 4.1 mg/L 9.3 mg/L
Sampled dosing regimen **2g q 8h** **2g q 12h** 1g q 6h 1g q 8h 1g q 12h Other	 **26 (37%)** **22 (31%)** 3 (4.3%) 8 (11.4%) 5 (7.1%) 6 (8.6%)	 **23 (40.4%)** **7 (12.3%)** 2 (3.5%) 15 (26.3%) 6 (10.5%) 4 (7.0%)
Receipt of prolonged infusion (defined as ≥3 hours)	57 (81.4%)	49 (85.9%)
Receipt of renal replacement therapy	6 (8.6%)	8 (14.0%)
Dose appropriate for renal function	**63 (90%)**	**51 (89.5%)**
Median # of Concomitant NT Rx/patient NT No NT	 **4** **4**	 **5** **6**

Figure 3. Adverse Neurologic Events and Attributable Neurotoxicity

Neurotoxicity	Cefepime N= 70 (%)	Meropenem N = 57 (%)
Any Adverse Neurologic Events	29 (41.4%)	30 (52.6%)
Attributable Rate of Neurotoxicity	**7 (10%)**	**3 (5.3%)**
NTAB review not indicated	42	27
Neurotoxicity Unlikely	21	27
Neurotoxicity Possible	3	2
Neurotoxicity Probable	**3**	**1**
Neurotoxicity Definitive	1	0
Description of Neurotoxicity Altered Mental Status Myoclonus	 6/7 (85.7%) 1/7 (14.3%)	 3/3 (100%) 0 (0.0%)

Figure 4. β-Lactam Exposures in Relationship to Attributable Neurotoxicity



Conclusion. Our study is the first to evaluate FEP NT prospectively and compare rates of NT to pts receiving MEM. We established criteria that were applied by a blinded NTAB. In doing so we found rates of NT to be lower than previously reported and not statistically different between FEP and MEM. Cmin values were highly variable and associated with numerically, but not statistically higher rates of NT for both agents. These findings serve as the basis for larger, multicenter studies and justify use of routine TDM to limit NT among high-risk pts.

Disclosures. **Brandon Smith, MD, PharmD**, **Shionogi** (Consultant, Advisor or Review Panel member) **Alexandra Urban, MD**, **Neuropace** (Consultant) **Ryan K. Shields, PharmD, MS**, **Shionogi** (Consultant, Research Grant or Support)

1101. Implementing a Beta-Lactam Therapeutic Drug Monitoring Program: Experience from a Large Academic Medical Center

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Session: P-62. PK/PD Studies

Background. Beta-lactams (BL) are the cornerstone of antimicrobial treatment for infections. Beta-lactam therapeutic drug monitoring (BL-TDM) optimizes drug concentrations to ensure maximal efficacy and minimal toxicity. The goals of this study were to describe the implementation process of a BL-TDM program and to further describe our experience using BL-TDM in clinical practice.

Methods. This was a retrospective review of adult patients with available BL-TDM between January 2016 and November 2019 at the University of Florida (UF) Health Shands Hospital. Total serum concentrations of BL were measured in the Infectious Diseases Pharmacokinetics Lab (IDPL) at UF, using a validated ultrahigh pressure liquid chromatography assay with triple quadrupole mass spectroscopy (LC-MS-MS). At our institution, TDM is available for 11 BLs and in-house assays are performed from Mon-Fri for most BLs.

Results. A total of 3,030 BL concentrations were obtained. An analysis was performed on the first BL-TDM encounter in 1,438 patients. The median age was 57 years (IQR, 41-69) and the median BMI was 27.5 kg/m^2 (IQR, 22.5-34.5). On the day of BL-TDM, the median serum creatinine was 0.83 (IQR, 0.59-1.30). Fifty-one percent of patients (n=735) were in an ICU at the time of BL-TDM with a median SOFA score of 6 (IQR, 3-9). BL-TDM was most frequently performed on cefepime (61%, n=882), piperacillin (15%, n=218), and meropenem (11%, n=151). The BL was administered as a continuous infusion in 211 (15%) patients. An interim analysis of 548 patients showed that BL-TDM was performed a median of 2 days (IQR, 1-4) from the start of BL therapy and resulted in a dosage adjustment in 26% (n=145).

Conclusion. BL-TDM was performed in older, non-obese patients with normal renal function. Over half of the evaluated patients were in an ICU at the time of TDM. This finding emphasizes the value of BL-TDM in the ICU setting because altered pharmacokinetics during critical illness has been linked to enhanced BL clearance. Interestingly, BL-TDM resulted in dosage adjustment in 1 in 4 patients who were receiving licensed BL dosing regimens, thus highlighting the role of TDM in dose individualization. BL-TDM was performed most commonly within the 72-hours of therapy initiation. Early BL-TDM has been shown to improve patient outcomes and should be promoted.

Disclosures. **Venugopalan Veena, PharmD**, **Melinta** (Other Financial or Material Support, Received a stipend for participation in a drug registry)**Merck** (Other Financial or Material Support, Received a stipend for participation in a drug registry) **Charles A. Peloquin, Pharm.D.**, Nothing to disclose

1102. Evaluation of Vancomycin Accumulation in Patients with Obesity

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Session: P-62. PK/PD Studies

Background. Current vancomycin guidelines recommend using actual body weight for dosing. However, in patients with obesity, this may result in lower initial vancomycin concentrations that can accumulate with continued doses due to differences in volume of distribution. The objective of this study is to evaluate the incidence of vancomycin accumulation in patients with obesity and identify potential factors associated with accumulation.

Methods. This is a single-center, retrospective, observational study at a tertiary academic medical center. Adult patients with a BMI ≥ 30 kg/m^2 and with ≥ 2 vancomycin serum trough concentrations within the same encounter in 2019 were screened. Patients were excluded if they were pregnant, had unstable renal function or severe renal impairment, received < 3 doses before a concentration was drawn, or had inconsistent dosing prior to a concentration draw. Linear kinetics were used to correct for differences in timing of concentration or dose changes. The major endpoint was the incidence of vancomycin accumulation, defined as a 20% increase in trough concentration between the first and any subsequent trough concentrations within the first 10 days of therapy. Minor endpoints included the percentage of supratherapeutic concentrations and the incidence of acute kidney injury (AKI). Descriptive statistics were used to evaluate endpoints and multivariable logistic regression was used to evaluate factors associated with accumulation.

Results. We screened 543 patients, and 162 were included in our analysis. The median age was 56.5 years (interquartile range [IQR] 43 - 65.3), and 62.3% were male. The