1314. Neonatal Serum Gentamicin Concentrations following Maternal Once-daily Gentamicin Dosing

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Session: P-59. PK/PD studies

Background. Gentamicin is commonly used for peripartum infections. Given literature supporting efficacy of once-daily dosing (ODD) of 5 mg/kg for chorioamnionitis, University of Chicago Medicine made the change from three times daily dosing (TIDD) to ODD. As gentamicin readily cross the placenta, it would be expected that maternal ODD would result in higher gentamicin neonatal serum concentrations following birth.

Methods. This was a single-center, retrospective chart review of all neonates born to mothers receiving peripartum ODD gentamicin within 12 hours of delivery between October 2019 and March 2020. A STAT random gentamicin serum concentration was obtained upon admission in neonates when initiation of antibiotics was desired. Specific dosing recommendations (Table 1) were developed utilizing neonatal population-based pharmacokinetics. The primary outcome was initial neonatal gentamicin serum concentration at birth. Other outcomes were also evaluated. Results were evaluated in two groups based on neonatal serum concentrations of less than 2 mcg/mL (Group 1) versus 2 mcg/mL or greater (Group 2).

Table 1: Neonatal gentamicin dosing algorithm

Gentamicin serum concentration (mcg/mL)	Birth weight < 2kg	Birth weight ≥ 2kg
≥ 6	36 hours after level, start gent 4 mg/kg q36h	24 hours after level, start gent 4 mg/kg q24h
4 to < 6	24 hours after level, start gent 4 mg/kg q36h	12 hours after level, start gent 4 mg/kg q24h
2 to < 4	12 hours after level, start gent 4 mg/kg q36h	6 hours after level, start gent 4 mg/kg q24h
< 2	NOW, start gent 4 mg/kg q36h	NOW, start gent 4 mg/kg q24h

Results: Thirty-two mother-newborn dyads were included in this study. Baseline demographics are shown in Table 2. Newborns had a median gestational age of 39.4 weeks and median birth weight of 3.39 kilograms. The mean initial gentamicin concentration was supratherapeutic at 3.06 + 1.92 mcg/mL among all newborns (Table 3). The mean maternal dose in Group 1 (n=11) was 3.52 mg/kg (3.34, 4.77) based on actual body weight and 4.78 mg/kg (4.34, 5.18) in Group 2 (n=21) (p=0.025). The median time between maternal gentamicin administration and time of delivery varied between the groups at 0.5 hours versus 2.63 hours, respectively (p=0.005). All newborn gentamicin concentrations were less than 2 mcg/mL for maternal doses given less than 1 hour prior to delivery (n=8) (Figure 1). Overall protocol compliance rate was 81.3%. There were no significant differences in nephrotoxicity or ototoxicity between groups.

Table 2. Baseline Demographics

Characteristics	All subjects (n=32)	Group 1 Gent < 2 (n=11)	Group 2 Gent > 2 (n=21)	*p*-value (Gent < 2 vs Gent ≥ 2)
Maternal				
Age (years)	29.19 ± 5.64	30.73 ± 5.44	28.38 ± 5.71	0.271
Actual Body Weight (kg)	79.0 (69.5, 90.0)	82.6 (67.1, 136.3)	78.0 (70.7, 84.8)	0.592
Gentamicin Dose (mg/kg) – Actual Body Weight	4.56 (4.03, 5.12)	3.52 (3.34, 4.77)	4.78 (4.34, 5.18)	0.025
Time between gentamicin administration and delivery (hours)	1.83 (0.78, 3.33)	0.50 (0.32, 1.37)	2.63 (1.72, 3.35)	0.005
Neonatal				
Gestational Age (weeks)	39.4 (37.4, 40.2)	39.1 (35.0, 40.3)	39.4 (38.6, 40.1)	0.842
Weight (kg)	3.39 (3.00, 3.73)	3.67 (2.98, 3.87)	3.37 (3.01, 3.70)	0.525
Sex (Male)	20 (62.5)	7 (63.6)	13 (61.9)	1.000
Time between delivery and serum gentamicin concentration (min)	43 (37, 64.5)	43 (36, 80)	43 (37, 64)	0.781
Other ototoxic medications during admission	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Other nephrotoxic medications during admission	1 (3.1)	1 (9.1)	0 (0)	0.344

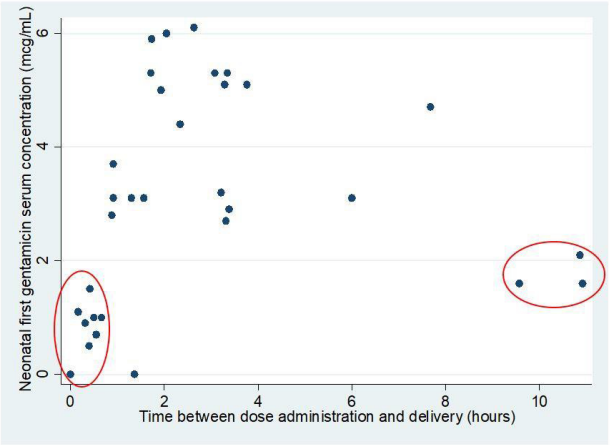
All data presented as n(%), median (IQR), or mean±SD

Table 3. Outcomes

Outcomes	All subjects (n=32)	Group 1 Gent < 2 (n=11)	Group 2 Gent > 2 (n=21)	*p*-value (Gent <2 vs Gent ≥ 2)
Initial serum gentamicin concentration (mcg/mL)	3.06 ± 1.92	0.90 ± 0.57	4.19 ± 1.27	< 0.0001
Compliance to Protocol	26 (81.3)	9 (81.8)	17 (81.0)	1.000
Failed initial hearing screen	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Failed repeat hearing screen	1 (3.1)	0 (0)	1 (4.8)	1.000
Serum creatinine increase by 0.3 mg/dL or ≥ 1.5x baseline in the first 7 days of life	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Positive blood culture within the first 72 hours of life • Organism • Days to clearance of culture	1 (3.1)	0 (0) N/A N/A	1 (4.8) E. coli (S to gent) 1 day	1.000
14-Day Mortality	0 (0)	0 (0)	0 (0)	1.000

All data presented as n(%) or mean±SD

Figure 1. Comparison of maternal gentamicin time from administration to delivery and neonatal serum gentamicin concentrations



Conclusion: This study suggests peripartum ODD of gentamicin may lead to clinically significant serum concentrations in neonates if administered between 1 to 12 hours of birth. Further studies are warranted to evaluate the effects of maternal ODD of gentamicin on newborns.

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

1315. No Dose Adjustment of Metformin with Fostemsavir Coadministration Based on Mechanistic Static and Physiologically Based Pharmacokinetic Models

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Session: P-59. PK/PD studies

Background. Fostemsavir (FTR) is an oral prodrug of the first-in-class attachment inhibitor temsavir (TMR) which is being evaluated in patients with multidrug resistant HIV-1 infection. In vitro studies indicated that TMR and its 2 major metabolites are inhibitors of organic cation transporters (OCT)1, OCT2, and multidrug and toxin extrusion transporters (MATEs). To assess the clinical relevance, of OCT and MATE inhibition, mechanistic static DDI prediction with calculated $I_{max,u}/IC_{50}$ ratios was below the cut-off limits for a DDI flag based on FDA guidelines and above the cut-off limits for MATEs based on EMA guidelines.

Methods. Metformin is a commonly used probe substrate for OCT1, OCT2 and MATEs. To predict the potential for a drug interaction between TMR and metformin, a physiologically based pharmacokinetic (PBPK) model for TMR was developed based on its physicochemical properties, in vitro and in vivo data. The model was verified and validated through comparison with clinical data. The TMR PBPK model accurately described AUC and C_{max} within 30% of the observed data for single and repeat dose studies with or without food. The SimCYP models for metformin and ritonavir were qualified using literature data before applications of DDI prediction for TMR

Results. TMR was simulated at steady state concentrations after repeated oral doses of FTR 600 mg twice daily which allowed assessment of the potential OCT1, OCT2, and MATEs inhibition by TMR and metabolites. No significant increase in metformin systemic exposure (AUC or C_{max}) was predicted with FTR co-administration. In addition, a sensitivity analysis was conducted for either hepatic OCT1 Ki, or renal OCT2 and MATEs Ki values. The model output indicated that, a 10-fold more potent Ki value for TMR would be required to have a ~15% increase in metformin exposure

Conclusion. Based on mechanistic static models and PBPK modeling and simulation, the OCT1/2 and MATEs inhibition potential of TMR and its metabolites on metformin pharmacokinetics is not clinically significant. No dose adjustment of metformin is necessary when co-administered with FTR

Disclosures. Xiusheng Miao, PhD, GlaxoSmithKline (Employee) Mindy Magee, Doctor of Pharmacy, GlaxoSmithKline (Employee, Shareholder) Peter D. Gorycki, BEChe, MSc, PhD, GSK (Employee, Shareholder) Katy P. Moore, PharmD, RPh, ViiV Healthcare (Employee)

1316. Pharmacokinetic/Pharmacodynamic Analyses of Cefiderocol in Critically Ill Patients

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Session: P-59. PK/PD studies

Background. Cefiderocol (CFDC), a novel siderophore cephalosporin, has demonstrated potent antibacterial activity against a wide range of Gram-negative bacteria including carbapenem-resistant strains. We aimed to evaluate relationships between drug exposure and outcomes in critically ill patients.

Methods. Sparse pharmacokinetic (PK) samples at steady state from critically ill patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection receiving CFDC in two Phase 3 studies were analyzed. Percent time of dosing interval of free drug concentration exceeding the minimum inhibitory concentration (MIC) in plasma and epithelial lining fluid (ELF) ($\%fT_{>MIC}$ and $\%fT_{>MIC,ELF}$, respectively) were determined for 60 (CREDIBLE-CR; NCT02714595) and 97 patients (APEKS-NP; NCT03032380), using a 3-compartment population PK model. The $\%fT_{>MIC,ELF}$ was calculated for 125 pneumonia patients based on an intrapulmonary PK model. Relationships between $\%fT_{>MIC}$, $\%fT_{>MIC,ELF}$ and clinical and microbiological outcomes at test of cure (TOC), or mortality at Day 28 were assessed.

Results. The median (90^{th} percentile) MICs of Gram-negative pathogens in the PK/pharmacodynamic (PD) analyses were 0.25 (4) µg/mL (CREDIBLE-CR) and 0.25 (2) µg/mL (APEKS-NP), respectively. Individual plasma $\%fT_{>MIC}$ was 100% in ≥95% of patients in each study, and estimated $\%fT_{>MIC,ELF}$ was 100% in 89.3% (25/28 pneumonia patients; CREDIBLE-CR) and 97.9% (95/97 pneumonia patients; APEKS-NP). Clinical cure rates and survival rates in patients with 100% $fT_{>MIC}$ or $\%fT_{>MIC,ELF}$ were similar between the two studies (Table). No PK/PD relationships between $\%fT_{>MIC}$, $\%fT_{>MIC,ELF}$ and clinical cure, microbiological eradication, or survival were identified in either study because high $\%fT_{>MIC}$ or $\%fT_{>MIC,ELF}$ was achieved in all patients.

Table. Clinical cure and survival rates in patients with 100% fT>MIC or %fT>MIC,ELF in CREDIBLE-CR and APEKS-NP studies

Table. Clinical cure and survival rates in patients with 100% $fT_{>MIC}$ or $\%fT_{>MIC,ELF}$ in CREDIBLE-CR and APEKS-NP studies

Study and outcome	$\%fT_{>MIC}$		$\%fT_{>MIC,ELF}$	
	<100%	100%	<100%	100%
CREDIBLE-CR, % (n/N)				
Clinical cure rate	0 (0/2)	62.1 (36/58)	0 (0/3)	64.0 (16/25)
Eradication rate	0 (0/2)	33.3 (25/75)	0 (0/3)	20.5 (8/39)
Survival rate	0 (0/2)	81.0 (47/58)	0 (0/3)	84.0 (21/25)
APEKS-NP, % (n/N)				
Clinical cure rate	100 (2/2)	65.3 (62/95)	100 (2/2)	65.3 (62/95)
Eradication rate	100 (2/2)	44.2 (53/120)	100 (2/2)	44.2 (53/120)
Survival rate	100 (2/2)	82.1 (78/95)	100 (2/2)	82.1 (78/95)

n=number achieving clinical cure, eradication, or survival; N=total number of patients for clinical outcome and mortality or total number of causative pathogens for microbiological outcome.

CREDIBLE-CR: n=60 (Median [Range] APACHE II score: 14 [2–29]). APEKS-NP: n=97 (Median [Range] APACHE II score: 15 [3–31])

Conclusion. PK/PD relationship was not identified between CFDC plasma or ELF exposure and clinical or microbiological outcomes, or mortality as high $\%fT_{>MIC}$ and $\%fT_{>MIC,ELF}$ were achieved, suggesting the recommended dosing regimen of 2 g q8h or renally adjusted dosage (including augmented renal clearance), infused over 3 hours, provides sufficient exposure to CFDC in critically ill patients.

Disclosures. Takayuki Katsube, PhD, Shionogi & Co., Ltd. (Employee) Nao Kawaguchi, BPharm, Shionogi & Co., Ltd. (Employee) Yuko Matsunaga, MD, Shionogi Inc. (Employee) Mari Ariyasu, BPharm, Shionogi & Co., Ltd. (Employee) Tsutae Den Nagata, MD, Shionogi & Co., Ltd. (Employee) Simon Portsmouth, MD, Shionogi Inc. (Employee) David Paterson, Accelerate (Speaker's Bureau)BioMerieux (Speaker's Bureau)BioMerieux (Advisor or Review Panel member)Entasis (Advisor or Review Panel member)Merck (Advisor or Review Panel member)Merck (Grant/Research Support)Merck (Speaker's Bureau)Pfizer (Speaker's Bureau)Shionogi & Co., Ltd. (Grant/Research Support)VenatoRx (Advisor or Review Panel member) Michael J. Satlin, MD, MS, Achaogen (Consultant)Allergan (Grant/Research Support)Merck (Grant/Research Support)Shionogi Inc. (Consultant) Roger Echols, MD, Shionogi Inc. (Consultant) Toshihiro Wajima, PhD, Shionogi & Co., Ltd. (Employee)

1317. Pharmacokinetics (PK) of Ampicillin-Sulbactam (SAM) during Orthotopic Liver Transplantation (OLT)

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Session: P-59. PK/PD studies

Background. SAM is used as surgical prophylaxis during OLT due to its broad spectrum activity against Gram-positive,-negative and anaerobic pathogens. SAM resistance among Gram-negatives is rising, making dosage selection paramount to preventing surgical site infections. Current guidelines recommend a 3g dose, consisting of 2g ampicillin (AMP) and 1g sulbactam (SUL), every 2h. There are no data; however, describing SAM PK during OLT to support an optimized dosing regimen.

Methods. This was a single-center PK study of OLT patients receiving SAM for surgical prophylaxis at a dose selected by the anesthesiologist. Patients were excluded if they were undergoing simultaneous liver and kidney transplantation and had a CrCL < 30 mL/min at start of surgery. Up to 24 blood samples, along with times of pertinent events, were collected throughout the OLT. AMP and SUL plasma concentrations were determined. Population PK analyses were conducted in Pmetrics using R. Akaike information criterion (AIC) and visual inspection determined best model fit. Individual PK parameters were simulated to describe free AMP time above the MIC_{90} ($fT>MIC_{90}$) of 32 mg/L.

Results. Five patients were enrolled. Participants had a mean ± SD age of 64 ± 7 years, body weight 82 ± 8 kg, CrCL of 75 ± 35 mL/min, and received various SAM doses (1.5-3g q2-3h). A 2 compartment model fitted the data better than a 1 compartment model for both AMP (AIC: 396 vs. 423) and SUL (AIC: 334 vs. 347). Final models included fractional clearance (CL_f) terms on typical total body clearance (CL_θ) to account for the placement of the portal vein clamp. AMP PK parameters (AIC: 372) were: CL_θ, 9.7 ± 2.6 L/h; CL_f, 0.73 ± 0.49; volume of central compartment (Vc), 7.2 ± 1.4 L; intercompartment constants (k12 and k21), 4.08 ± 3.28 and 2.63 ± 2.9 h^{-1}, respectively. Final SUL PK parameters (AIC: 314) were: CL_θ, 8.3 ± 2.5 L/h; CL_f, 0.92 ± 0.55; Vc, 7.3 ± 1.6 L; k12, 4.60 ± 4.41 h^{-1}, and k21, 4.07 ± 3.31 h^{-1}. Exposures ranged from 58-96% with only 3g q2h providing nearly 100% $fT>MIC_{90}$.

Conclusion. This is the first study to describe intra-operative SAM PK in OLT recipients and the effect of portal vein clamp on AMP and SUL clearance. These data will help guide optimized SAM dosing regimens for OLT surgery based on local MIC distributions for targeted pathogens.

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1318. Pharmacokinetics and Safety of Cefepime-Taniborbactam (formerly Cefepime/VNRX-5133) in Subjects with Renal Impairment

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Session: P-59. PK/PD studies

Background. Taniborbactam is a novel, non-ß-lactam, ß-lactamase inhibitor with activity against serine (Class A, C, D) and metallo (Class B) ß-lactamases including epidemiologically important carbapenemases. Both cefepime and taniborbactam are predominantly renally excreted and are likely to require dose adjustment in patients with renal impairment and end-stage renal disease (ESRD). The current study was designed to evaluate the pharmacokinetics and safety in patients with renal impairment and ESRD.

Methods. This was a Phase 1, open-label study in subjects with normal renal function (eCL_{CR} ≥ 90 mL/min) matched to subjects with mild, moderate, and severe renal impairment (eGFR 60-89, 30-59, and < 30 mL/min/1.73m^2, respectively), and patients with ESRD on hemodialysis. Subjects received a single dose of cefepime 2 g and taniborbactam 500 mg; subjects with ESRD received a single dose before HD and after a 9 day washout period, following HD. PK parameters including $AUC_{0\text{-}inf}$ and total body clearance (CL) were evaluated. Safety assessments included adverse events (AEs), vital signs, clinical laboratory evaluations, electrocardiograms, and physical examinations.

Results. Thirty-three subjects were enrolled; 67% male, 58% white and 39% black/African Americans. Median age and BMI were 55.0 years and 29.5 kg/m^2, respectively. For both cefepime and taniborbactam, exposures increased, and CL decreased with increasing renal impairment (see Table). The hemodialysis extraction ratio was 49.7% and 47.4% for taniborbactam and cefepime respectively. No safety signals were observed and there were no serious adverse events.

Table

	Taniborbactam		Cefepime	
Renal Function Group (eGFR range [mL/min])	**$AUC_{0\text{-}inf}$ (h*µg/mL) Mean (SD)**	**CL (L/h) Mean (SD)**	**$AUC_{0\text{-}inf}$ (h*µg/mL) Mean (SD)**	**CL (L/h) Mean (SD)**
Normal (≥ 90)	**84.1 (9.7)**	**5.83 (0.66)**	**345.8 (45.9)**	**5.69 (0.75)**
Mild (60-89)	**97.9 (11.1)**	**4.99 (0.70)**	**419.5 (37.7)**	**4.64 (0.54)**
Moderate (30-59)	**229.8 (50.2)**	**2.17 (0.55)**	**927.9 (182.1)**	**2.13 (0.48)**
Severe (<30)	**557.5 (462.6)**	**1.30 (0.73)**	**1,891.4 (1330.1)**	**1.41 (0.74)**

Conclusion: Cefepime and taniborbactam CL is similarly reduced with varying degrees of renal impairment. Dialysis removes a high fraction of both drugs. Dose adjustments recommended for cefepime are appropriate for taniborbactam.

Disclosures. Brooke Geibel, BS, Venatorx Pharmaceuticals (Employee, Shareholder) James A. Dowell, PhD, Venatorx Pharmaceuticals (Independent Contractor) Thomas C. Marbury, MD, Venatorx Pharmaceuticals (Independent Contractor) William Smith, MD, Venatorx Pharmaceuticals (Independent Contractor) Paul C. McGovern, MD, Venatorx Pharmaceuticals (Employee) Cynthia Richards, MD, Venatorx Pharmaceuticals (Independent Contractor) Tim Henkel, MD, PhD, Venatorx Pharmaceuticals (Employee, Shareholder)

1319. Pharmacokinetics of Ceftolozane/Tazobactam in Patients with Burns

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