1382. Acute Kidney Injury with Piperacillin–tazobactam and Vancomycin in the Intensive Care Unit

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Background. Several recent retrospective studies have suggested that the combination of vancomycin (V) with piperacillin–tazobactam (PTZ) is associated with increased nephrotoxicity. We prospectively evaluated the outcomes of patients admitted to all of our medical and surgical intensive care units (ICU) with a normal baseline creatinine clearance (CrCl) that received vancomycin in combination with either cefepime (CEF) or PTZ to determine whether kidney injury occurs using RIFLE criteria.

Methods. ICU patients who received combinations of V with either PTZ or CEF were prospectively evaluated from June 1, 2017 to April 28, 2018 using Theradoc. V and PTZ dosing were standardized per ICU policy and monitored by clinical pharmacists. We included patients between ages 18 and 90, and receipt of >72 hours of combination antibiotic therapy. We excluded patients that were pregnant, had a hematologic malignancy, chronic kidney disease, or neuromuscular disease. Data collected included, CrCl, V troughs, dosage and length of all antibiotics used, ICU length of stay (LOS), and co-administered nephrotoxic medications (e.g., NSAIDs and IV contrast). The primary objective was to compare the incidence of AKI in these study groups, as defined by the RIFLE criteria.

Results. Of 233 patients evaluated, 58 (25%) met inclusion criteria, 45 received PTZ-V and 13 CEF-V. Only eight of 58 (14%) MRSA-positive culture.

Table 1: Data Summary

	PTZ-V	CEF-V	*P*-value
Age (median, range)	58 (35–84)	64 (18–79)	0.54
Gender (male)	30 (67%)	7 (54%)	0.51
Median weight (kg)	86 (54–136)	82.4 (51–156)	0.6
No > 100 kg	11 (24%)	3 (23%)	1
No V trough >20	2 (4%)	1 (8%)	0.6
Median V trough(range)	11.4 (5.4–32.7)	10.6 (6.4–29.5)	0.695
Median V days (range)	5 (3–16)	4 (3–13)	0.99
Co-admin nephrotoxic agent	41 (91%)	11 (85%)	0.61
ICU LOS	11 (4–36)	14 (3–32)	0.35
Hospital LOS	15 (4–36)	20 (6–72)	0.037
No. AKI by RIFLE	13	0	0.028

We found no correlation with co-administered nephrotoxic agents, vancomycin troughs, or body weight and AKI.

Conclusion. Our prospective observational study data revealed significant AKI with PTZ-V compared with CEF-V but it did not impact patient long-term outcomes. Caution with PTZ-V may be required when used in ICU settings even in patients with normal baseline CrCl.

Disclosures. **J. S. Lewis II**, Merck: Consultant, Consulting fee.

1383. *In vivo* Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of NOSO-502, a First-in-Class Odilorhabdin Antibiotic, Against *E. coli* (EC) and *K. pneumoniae* (KPN) in the Murine Neutropenic Thigh Model

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Background. NOSO-502 is a novel, first-in-class Odilorhabdin antibiotic targeting bacterial protein translation, with potent *in vitro* activity against *Enterobacteriaceae* including strains with MDR or CRE-phenotype. The goal of this study was to determine the PK/PD characteristics of NOSO-502 using the murine thigh infection model against a diverse group of EC and KPN strains.

Methods. Twelve strains (6 EC, 6 KPN) were utilized, including those with tetracycline or β-lactam resistance. MICs were determined by CLSI Methods. Single dose murine plasma PK of NOSO-502 was determined after administration of 7.81, 31.25, 125 and 500 mg/kg by SC route. Dose fractionation (DF) study was used to determine which PK/PD index was associated with efficacy. The relationship between each PK/PD indices and CFU outcome data were analyzed using the sigmoid Emax (Hill) model with nonlinear regression. Treatment studies were then performed with the remaining 11 strains. Four-fold increasing NOSO-502 doses (3.91–1,000 mg/kg/6 hours SC route) were administered. Treatment data and AUC/MIC was analyzed to determine AUC/MIC targets associated with net stasis and 1-log kill (when achieved) for all strains.

Results. MICs ranged from 1 to 4 mg/L. PK ranges for doses included: Cmax 1.5–85 mg/L, $AUC_{0-\infty}$ 1.9–352 mg hour/L, T1/2 0.4–1.1 hour. DF regression analysis: AUC/MIC R^2 0.86, Cmax/MIC R^2 0.70, $T >$ MIC R^2 0.77. Against each of the 12 strains there was dose-dependent activity and net stasis was achieved against all strains, with maximal activity of 1–2 log killing in EC and almost 3 log killing in KPN. The 24 hours stasis total and free drug PD targets are shown (table). 1-log kill targets were determined for KPN and noted at a median 24 hours fAUC/MIC of 11.

		24 hours Static Dose (mg/kg)	Stasis tAUC/MIC	Stasis fAUC/MIC
EC	Mean	374	53	10
	Median	409	59	12
	SD	182	32	6.3
KPN	Mean	81	21	4.2
	Median	56	9.1	1.8
	SD	56	24	4.7

Conclusion. NOSO-502 demonstrated in vivo potency against a diverse group of EC and KPN strains including those with resistance to tetracycline and β-lactams. The PK/PD index predictive of efficacy is AUC/MIC. Stasis 24 hours AUC/MIC targets were numerically low for KPN and EC. This data suggest that NOSO-502 is a promising novel agent and these targets will provide a basis for developing human dosing regimens to optimize efficacy.

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1384. RSV Monoclonal Antibody (MK-1654) Phase 1 Pharmacokinetics (PK) in Healthy Adults and Population PK Modeling to Support Pediatric Development

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Background. Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection and hospitalization in infants. MK-1654 is a monoclonal antibody (mAb) being developed to prevent RSV infection in infants and is undergoing evaluation in a Phase 1 study. Incorporation of YTE mutations extend its half-life to allow for dosing once every RSV season. Preliminary Phase 1 PK results and the development of a population PK model that characterizes adult PK to predict pediatric exposures are presented here.

Methods. In this double-blinded Phase 1 study, 152 healthy males and females of nonchildbearing potential aged 19–59 years were randomized in a 3:1 ratio to receive a single dose of MK-1654 or placebo as a bolus intramuscular injection (IM) or in an intravenous infusion (IV) over 2.5 hours. Dose levels included 100 mg IM, 300 mg IM, 300 mg IV, 1,000 mg IV and 3,000 mg IV. Serial serum samples were collected to measure MK-1654 PK via a validated LC/MS assay. A noncompartmental PK analysis was conducted using preliminary data from 60 subjects up to Day 150 (900 observations). A population PK model was developed to simultaneously characterize the IM and IV adult PK data and to predict pediatric PK through allometric scaling. Pediatric MK-1654 PK was predicted for several IM doses for a typical sized infant (35 weeks gestational age at birth; 4 months chronological age at dosing; 50th percentile weight).

Results. In adults, the median time to maximum concentration observed was ~6–10 days following IM injection. The apparent half-life of MK-1654 ranged from ~70–85 days after either IM or IV doses. The estimated IM bioavailability was ~71%. C_{max} and $AUC_{0\text{-}90\ days}$ increased dose proportionally following IV administration. MK-1654 adult PK was best characterized using a two-compartment model with first-order elimination. IM absorption was described using a first-order rate constant with lag time. Inter-individual variability was included for clearance (CL and Q), central volume (V2), and absorption rate (Ka). The pediatric model suggested apparent terminal half-life in a typical infant is shorter than adults, likely being driven by infant growth during treatment.

Conclusion. Predicted infant PK profiles support further development of MK-1654 in children.

Figure 1: Mean ± Standard Deviation Serum Concentration-Time Profiles in Healthy Adults (n=12/panel) Following a Single Dose of MK-1654

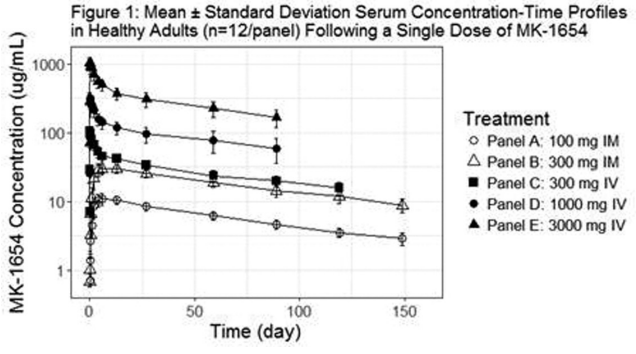

Table 1: MK-1654 PN001 Interim PK NCA Summary for Adults

Panel	Dose (mg)	Route	T_{last} (day)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (day*µg/mL)	AUC_{0-90d} (day*µg/mL)	T_{max} (day)	$t_{½}$ (day)
A	100	IM	150	11.1 (18.1)	1,170 (16.3)	644 (12.3)	6.00 (2.00 - 13.0)	77.6 (16.4)
B	300	IM	150	31.2 (11.6)	3,670 (18.6)	1,910 (12.8)	9.50 (4.00 - 27.0)	82.4 (22.5)
C	300	IV	120	107 (12.3)	5,190 (19.2)	2,750 (13.2)	0.167 (0.104 - 0.167)	85.1 (25.8)
D	1000	IV	90	326 (18.7)	14400 (49.8)	8,080 (29.0)	0.167 (0.104 - 0.333)	76.8 (53.7)
E	3000	IV	90	1050 (15.8)	42,100 (29.0)	25,500 (22.0)	0.167 (0.104 - 0.167)	69.5 (20.0)

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1385. Efficacy of Ceftazidime–Avibactam in Combination with Aztreonam (COMBINE): Solutions for Metallo-β-Lactamase Producing-Enterobacteriaceae (MBL)

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Background. Novel antibiotics will not be available to combat the threat of MBLs until 2021. One strategy to overcome MBLs is to combine CAZ-AVI + ATM. ATM is not hydrolysed by MBLs and AVI offers protection for ATM and CAZ vs. ESBLs and AmpCs. The combination also offers a theoretical advantage to inactivating multiple PBPs by using dual β-lactam therapy. Our objective was to define optimal dosing profiles for clinical use of ATM to add to CAZ-AVI in the hollow fiber infection model (HFIM).

Methods. *E. coli* ARLG-1013 (bla_{NDM-1}, bla_{CTX-M}, bla_{CMY}, bla_{TEM}) and *K. pneumoniae* ARLG-1002 (bla_{NDM-1}, $bla_{CTXM-15}$, bla_{DHA}, bla_{SHV}, bla_{TEM}) were studied at a 7.5 $\log_{10}$ CFU/mL in the HFIM. Human dosing regimens of CAZ-AVI 2 g/0.5 g q8h (2 hours infusion) and ATM 2 g q8h (2 hours infusion) were simulated in alone and in combination. Continuous infusion (CI) regimens of CAZ-AVI 6 g/1.5 g per day CI + ATM 6 g/day CI and q8h regimens were given simultaneously and sequentially (ATM given 2 hours after CAZ-AVI). Resistant subpopulations were profiled on single (ATM), double (CAZ/AVI) and triple (ATM/CAZ/AVI) drug plates containing 2/2/4, 8/8/4, or 32/32/4 mg/L over 7 days.

Results. Against *E. coli* ARLG-1013, ATM alone mirrored growth control (+3.14 at 168 hours) (All units Log_{10} CFU/mL change vs. baseline). CAZ-AVI alone showed some intrinsic activity (+1.19 at 168 hours). CAZ-AVI 2g/0.5g q8h (2 hours infusion) + ATM 2g q8h (2 hours infusion) given sequentially resulted regrowth and stasis (+0.34 at 168 hours) vs. the simultaneous combination resulted initial bactericidal activity (-3.53 killing within 28 hours) which regrew at (–0.90 at 168 hours). All CI regimens were effective. CAZ-AVI 6g/1.5g per day CI + ATM 6 g/day CI resulted in dramatic killing (up to -5.78 killing within 50 hours) which was sustained (up to -3.90 killing at 168 hours). Comparing the infusion time of CAZ/AVI + ATM on bacterial killing: CI + CI > 2 hours + 2 hours > 30 minutes + 30 minutes. CI + CI resulted in complete suppression of resistance over 7 days. Against *K. pneumoniae* ARLG-1002, CAZ/AVI (CI) + ATM (CI) resulted in early synergy (>5.0 log killing within 24 hours) and suppression of resistance for more than 168 hours.

Conclusion. The combination of CAZ-AVI + ATM was highly synergistic and suppressed resistance against MBL Enterobacteriaceae in HFIM. ATM efficacy in combination was driven by %*T* > MIC. A Phase I study will assess safety to provide patients a critically important solution against "untreatable" Gram negatives.

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1386. Efficacy of Repeat Dosing of Oral Fosfomycin in a Dynamic Bladder Infection *In Vitro* Model

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Background. Oral fosfomycin is indicated for uncomplicated urinary tract infections with activity against MDR-uropathogens. Despite off-label use of giving three doses every 2–3 days, limited supporting data are available. We performed pharmacodynamic profiling using a dynamic bladder infection *in vitro* model to assess adequacy of repeat doses of fosfomycin.

Methods. A bladder infection *in vitro* model simulating urinary fosfomycin concentrations after 3 g (equiv.) oral doses was used with Mueller–Hinton broth (MHB) with 25 mg/L glucose-6-phosphate. Fosfomycin exposures were validated by LC–MS/MS measurements. Pharmacodynamic response of 16 clinical Enterobacteriaceae isolates were examined (eight *E. coli*, four *E. cloacae*, four *K. pneumoniae*; agar dilution MIC 0.25–64 mg/L) following three doses of fosfomycin given every 72, 48 or 24 hours, compared with single dose therapy. Pathogen kill and resistance was assessed by quantitative cultures on drug-free and fosfomycin-containing Mueller–Hinton agar (MHA +64 mg/L, +512 mg/L).

Results. Fosfomycin exposure following single and multiple doses were accurately reproduced (mean deviation from target 5.0 ± 3.4%, max 11.8%) with minimal variability (mean relative SD 2.7 ± 1.7%, max 8.8%). Fosfomycin high-level heteroresistance was detected prior to drug exposure in 8/16 isolates (proportion 0.00002–0.001% of total population). All isolates with high-level heteroresistance regrew following single dose fosfomycin. Following three doses given every 72 hours, one additional *K. pneumoniae* isolate was killed. All other isolates regrew with amplification of HLR subpopulation (median proportion: 71.4%, IQR 57.5–100%). Despite dosing 48 and 24 hourly, the same isolates regrew, although HLR subpopulation amplification was reduced (48 hours dosing: 32.0%, IQR 0.005–83.3%; 24 hours dosing: 0.3%, IQR 0.0004–81.3%).

Conclusion. Dynamic *in vitro* modeling of multiple doses of oral fosfomycin fails to additionally suppress regrowth in the majority of isolates compared with single dose therapy. Baseline high-level heteroresistance is an important predictor for regrowth. These results suggest that giving multiple doses of fosfomycin is not necessarily better than standard single dose therapy. Earlier timing of repeat doses may help suppress the emergence of resistance.

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1387. Phase I Study to Evaluate the Safety and Pharmacokinetics (PK) of Single and Multiple Ascending Doses (SAD/MAD) of Intravenous (IV) Minocycline in Healthy Adult Subjects

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Background. Carbapenem-resistant *Acinetobacter baumannii* infections are defined by the WHO as a critical threat. IV minocycline is approved in the United States for treatment of *Acinetobacter* infections at doses up to 200 mg BID. This study investigated safety and PK of single and multiple doses of IV minocycline, including doses higher than approved in the United States.

Methods. This was a randomized, double blind, placebo-controlled, SAD/MAD study of 6 doses (100–600 mg) of IV minocycline. Healthy adult subjects received a single dose of minocycline or placebo on Day 1, and 15 doses BID starting on Day 4. Safety was assessed throughout the study. Serial blood and urine samples were collected for PK assessment.

Results. Sixty-nine healthy subjects were randomized, 49 were included in the PK analysis. No serious adverse events (AEs) occurred; 55 subjects (79.9%) reported study drug-related AEs; dizziness 40 (58.0%) and nausea 34 (49.3%) were the most common. All related AEs were mild except for seven subjects with moderate nausea and/or dizziness. Dosing in the 400 mg cohort was discontinued due to AEs, therefore MAD escalation was stopped. Subsequent cohorts were escalated for SAD and loading dose only.

SAD Mean (SD) PK Parameters

Dose (mg)	100	200	300	400	500	600
N	8	8	8	8	8	9
Cmax (mg/L)	0.99 (0.2)	1.89 (0.4)	3.35 (1.2)	4.93 (1.8)	4.36 (0.9)	7.03 (2.4)
$T_{1/2}$ (h)	11.05 (2.1)	13.70 (2.3)	16.62 (3.9)	17.55 (2.1)	14.44 (2.7)	17.27 (3.6)
$AUC_{0-\infty}$(mg*h/L)	9.73 (1.4)	25.90 (6.9)	39.16 (13.8)	63.64 (18.2)	53.76 (20.3)	83.00 (29.4)
Cl (L/h)	10.48 (1.8)	8.21 (2.2)	8.28 (2.1)	6.71 (1.7)	10.25 (3.0)	8.07 (2.8)
Vss (L)	156 (36.7)	148 (36.6)	158 (45.4)	142 (38.0)	179 (46.5)	153 (52.8)

AUC, area under the drug concentration–time curve; Cmax, maximum observed drug concentration; $T_{1/2}$, half-life; Cl, plasma clearance; Vss, volume of distribution at steady state. *N*, number of subjects.

Conclusion. Single IV doses of minocycline up to 600 mg were tolerated reasonably well, but the maximum tolerated multi-dose was 300 mg BID. Most common AEs were mild nausea and dizziness with evidence of increasing incidence but not increasing severity with increasing dose. Exposure increased in a dose proportional fashion with exception of the 500 mg dose. The dosage regimen selected for further studies will be a 600 mg loading dose followed by 300 mg BID.

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