after being dosed. Part 2: PK was linear with doses in the range of 1500–3000 mg. Administration of gepotidacin 3000 mg tablets in the fed state slightly reduced C_{max} and slightly increased AUC at the 3000 mg dose level. The 1500 and 2250 mg doses were tolerated while the 3000 mg dose was better tolerated compared to the fasted state with fewer and short-lived GI AEs, mostly mild in intensity. After oral administration of 1500–3000 mg, high urine drug concentrations were achieved, remaining above the minimum inhibitory concentration of 4 µg/mL for up to 24 hours.

Conclusion. The PK of gepotidacin following administration of a single oral dose to Japanese subjects was linear from 1500–3000 mg and food decreased C_{max} without impact on exposure (AUC). Administration of gepotidacin with food resulted in an improved GI tolerability profile at the higher dose tested in Japanese subjects.

Disclosures. **Mohammad Hossain, PhD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Courtney Tiffany, BSc**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Aline Barth, MSC;PHD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Employee of and shareholder in GlaxoSmithKline plc.) **Aparna Raychaudhuri, Ph.D.**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and past/current shareholder in GlaxoSmithKline plc.) **Etienne F. Dumont, MD**, **GlaxoSmithKline plc.** (Employee, Shareholder, Former employee of and shareholder in GlaxoSmithKline plc.)

1117. Tazobactam Pharmacokinetic/Pharmacodynamic Target Attainment in Healthy Volunteers and Critically-Ill Hospitalized Patients

Shamir N. Kalaria, PharmD, PhD[1]; Jason M Pogue, PharmD, BCPS, BCIDP[2]; Emily Heil, PharmD, MS, BCIDP[3]; Emily Heil, PharmD, MS, BCIDP[3]; [1]University of Maryland Medical Center, Baltimore, Maryland; [2]College of Pharmacy, University of Michigan, Ann Arbor, Michigan; [3]University of Maryland School of Pharmacy; University of Maryland Medical Center, Baltimore, MD

Session: P-62. PK/PD Studies

Background. Pharmacokinetic/pharmacodynamic (PK/PD) targets and attainment are well described for beta-lactams; however, are rarely considered for beta-lactamase inhibitors. Recent evidence suggests that tazobactam (TAZ) target exposures to restore piperacillin bacteriostatic and 1 log 10 bactericidal activity against Enterobacterales are fT> the piperacillin/tazobactam (TZP) MIC of 64% and 77%, respectively. The aim of this study was to evaluate TAZ probability of target attainment (PTA) of a 500 mg every 6-hour dose of tazobactam using population PK data in both healthy volunteers and hospitalized patients.

Methods. PK exposures in 1,000 patients with varying degrees of renal function were simulated using a previously described TAZ PK model developed with data from critically ill infected patients. An identical one-compartment structural model describing TAZ PK using mean population parameters observed in phase 1 PK studies was also used to simulate exposures in healthy volunteers. All simulated patients received 500 mg of TAZ as an intravenous infusion over 30 minutes or as a 3-hour extended-infusion.

Results. The table displays PTA results for patients with an estimated creatinine clearance of 60 mL/min. Based on healthy volunteer data, the highest TZP MIC where ~90% PTA was achieved for bacteriostasis was 1 mg/L and was 0.25 mg/L for bactericidal activity. These were only achieved with extended infusion administration of TAZ. In the cohort of hospitalized patients, >90% PTA of TAZ exposures associated with both bacteriostasis and 1 log kill were achieved up to a MIC of 2 for intermittent infusion and up to 4 mg/L for extended infusion, due to decreased TAZ clearance in hospitalized patients. These values are significantly lower than the CLSI TZP susceptibility breakpoint of 16 mg/L, and PTA rates were lower at increased creatinine clearances.

Table: Percent Target Attainment of Tazobactam exposures associated with restoring bacteriostasis (fT> MIC of 64%) and bactericidal activity (fT> MIC of 77%) of piperacillin in simulated patients receiving 500 mg every six hours of tazobactam with a creatinine clearance of 60 mL/min

TZP MIC	Healthy Volunteer		Critically-Ill Hospitalized Patients	
fT>MIC of 64%	30-min infusion	3-hour infusion	30-min infusion	3-hour infusion
0.25	82	98	100	100
0.5	78	96	99	100
1	71	93	98	100
2	60	87	94	99
4	41	72	84	96
8	14	37	51	79
16	1	6	<1	6
fT>MIC of 77%				
0.25	77	92	99	100
0.5	71	89	97	100
1	63	83	95	99
2	50	73	90	97
4	30	51	77	90
8	8	21	41	62
16	0.5	3	0	0

Conclusion. fT>TZP MIC target attainment is poor with maximal package insert tazobactam doses given with piperacillin, even when administered as an extended infusion. These findings have serious implications for the role of TZP in beta-lactamase producing Enterobacterales, including ESBLs, and suggest the current susceptibility breakpoints are 4-32 fold higher than those supported by PK/PD data.

Disclosures. **Jason M Pogue, PharmD, BCPS, BCIDP**, **Merck** (Consultant)**QPex** (Consultant)**Shionogi** (Consultant)**Utility Therapeutics** (Consultant)**VenatoRX** (Consultant) **Emily Heil, PharmD, MS, BCIDP**, Nothing to disclose

1118. Population Pharmacokinetics of Contezolid Acefosamil and Contezolid – Rationale for a Safe and Effective Loading Dose Regimen

Jürgen B. Bulitta, PhD[1]; Barry HAFKIN, MD[2]; Edward Fang, MD[3]; [1]University of Florida, Orlando, Florida; [2]MicuRx Pharmaceuticals / Consultant, Austin, Texas; [3]MicuRx Pharmaceuticals, San Carlos, California

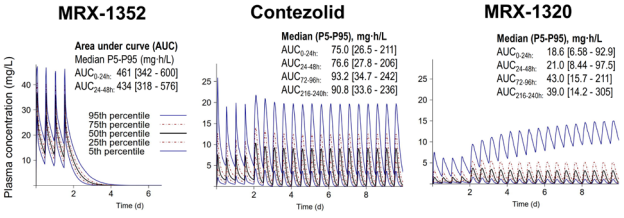
Session: P-62. PK/PD Studies

Background. Contezolid (CZD) is a novel oral oxazolidnone with comparable activity and potentially improved safety compared to current oxazolidinones. The intravenous (IV) double prodrug contezolid acefosamil (CZDa) is converted via MRX-1352 to active CZD. CZDa paired with CZD holds promise as a safe and effective treatment for serious Gram-positive infections such as those caused by methicillin-resistant *Staphylococcus aureus*. Sequential therapy with CZDa IV followed by CZD oral (PO) offers flexible treatment options in hospital and outpatient settings for conditions such as diabetic foot infections. We aimed to design a CZDa/CZD dosage regimen leveraging population pharmacokinetic modeling (PopPK).

Methods. PopPK simultaneously fit data from 184 adult subjects. These were 1) plasma concentrations (by LC-MS/MS) of MRX-1352, CZD, and its metabolite MRX-1320 from 66 healthy subjects receiving CZDa (150-2400 mg IV) for up to 10 days, 2) CZD and MRX-1320 concentrations from 44 healthy subjects receiving single CZD PO doses of 400, 800, or 1200 mg with and without food or multiple doses Q12h for up to 28 days, and 3) CZD concentrations from 74 Phase 2 patients receiving CZD 800 mg PO Q12h. PopPK and Monte Carlo simulations were used to optimize CZD exposures.

Results. CZDa was rapidly converted to MRX-1352, which was converted less rapidly to CZD. CZD was well absorbed and food enhanced its bioavailability. For CZD 800 mg PO with food, apparent total clearance of CZD was 13.1 L/h (22% coefficient of variation) in healthy subjects and 14.5 L/h (53% CV) in patients. The apparent volume of distribution at steady-state was 20.5 L. A loading dose of CZDa 2000 mg IV, then CZDa 1000 mg IV Q12h, and followed by CZD 800 mg PO Q12h achieved areas under the curve (AUC) between 75 and 100 mg*h/L (medians; Figure) on all study days. Compared to CZD AUCs, the MRX-1352 AUCs during IV dosing were higher. While the median MRX-1320 AUCs were lower (18 to 48 mg*h/L), some accumulation was predicted in ~5% of subjects.

Figure: Monte Carlo simulation of contezolid acefosamil 2000 mg IV at 0 h, then 1000 mg IV at 12, 24 & 36 h, followed by 800 mg oral contezolid Q12h



Conclusion. A loading dose of CZDa 2000 mg IV followed by either CZDa 1000 mg IV or CZD 800 mg PO Q12h was predicted to reliably achieve efficacious CZD exposures on day 1 and maintain those exposures throughout therapy. This regimen will be evaluated in Phase 3 studies in complicated skin infections and diabetic foot infections.

Disclosures. **Jürgen B. Bulitta, PhD**, **MicuRx Pharmaceuticals, Inc.** (Consultant) **Barry HAFKIN, MD**, **MicuRx Pharmaceuticals Inc.** (Consultant)

1119. Assessment of Vancomycin Pharmacokinetic Parameters in Pediatric Patients After Liver Transplantation

Ronaldo Morales Junior[1]; Vanessa D. Juodinis, n/a[2]; Daniela Carla de Souza, n/a[2]; Silvia Regina C. Jorge Santos, n/a[1]; [1]São Paulo University, São Paulo, Sao Paulo, Brazil; [2]Sírio-Libanês Hospital, São Paulo, Sao Paulo, Brazil

Session: P-62. PK/PD Studies

Background. Vancomycin is largely prescribed to treat gram-positive bacterial infections in pediatric patients after liver transplantation with the same empirical doses prescribed in other critical conditions due to the absence of pharmacokinetic studies in this population. The objective of this investigation was to describe the vancomycin pharmacokinetic parameters and to assess the vancomycin percentage of target attainment with empirical regimen.

Methods. Prospective and longitudinal study with pediatric post-liver transplantation patients who received at least 48 hours of vancomycin between January 2020 and May 2021. Patients with acute or chronic renal failure or receiving renal replacement therapy were excluded. Vancomycin therapy started with 40-60mg/kg daily, one-hour infusion. The pharmacokinetic parameters were determined by one-compartment model with first-order kinetics using near steady-state postdistributional peak and trough within the same dosing interval. Therapeutic target was defined as vancomycin 24-hour area under the curve/minimum inhibitory concentration (AUC^{ss}_{0-24}/MIC) ≥ 400 and < 600. The study protocol was approved by the local ethics committee.

Results. We included 18 sets of peak/trough serum concentrations obtained from 12 patients. The patients had median age of 11 (interquartile range [IQ] 8-16) months. The found vancomycin clearance, volume of distribution and half-life values were,