1400. Mass Balance, Metabolism, and Excretion of [14C]-Plazomicin in Healthy Human Subjects

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Background. Plazomicin is a next-generation aminoglycoside (AG) with a structure that protects it from common AG resistance mechanisms in Enterobacteriaceae and with in vitro activity against extended spectrum β-lactamase-producing and carbapenem-resistant Enterobacteriaceae. The purpose of this study was to evaluate the metabolism and excretion of plazomicin in healthy human subjects.

Methods. Six healthy male subjects were administered a single 30-minute intravenous infusion of 15 mg/kg [14C]-plazomicin (~100 µCi/dose). Following administration, blood (and plasma), urine, and feces were collected for 7 days. Total radioactivity was analyzed by liquid scintillation counting; plazomicin concentration was analyzed by a validated liquid chromatography–tandem mass spectrometry method; and metabolite profiling was conducted by accelerator mass spectrometry (AMS).

Results. The majority of the total administered radioactivity was recovered in urine (88.1%), with negligible amounts (~0.2%) excreted in feces. Radioactivity was rapidly eliminated with ~56% of the total radioactivity recovered in urine within the first 4 hours postdose and >85% recovered in urine by 48 hours postdose. Analysis of nonradioabeled plazomicin demonstrated that 97.5% of the dose was recovered as unchanged parent drug in urine by the end of the last sampling interval. Metabolite profiling of plasma at 10 hours postdose using AMS showed that plazomicin was the only definable peak present, accounting for 94.3% and 93.6%, respectively, of the total carbon content.

Conclusion. Mass balance was achieved for [14C]-labeled and for nonradioabeled plazomicin as the majority of the administered dose was recovered in urine, with negligible amounts in the feces. Plazomicin was eliminated as unchanged drug by the kidneys and thus did not appear to be metabolized to any appreciable extent. No metabolites were detected by AMS and plazomicin was the only definable peak present in plasma and urine.

Disclosures. T. Choi, Achaogen, Inc.; Employee, Salary. J. D. Serogy, Achaogen, Inc.; Employee and Shareholder. S. Sanghvi, Xceleron; Employee, Salary. V. Dhuria, Achaogen, Inc.; Employee, Salary.

1402. Cystatin C Improves Estimation of Vancomycin Clearance in Critically Ill Children Using a Population Pharmacokinetic Modeling Approach

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Background. Vancomycin (VAN) is renally eliminated and clearance (CL) correlates with glomerular filtration rate (GFR). The bedside Schwartz equation predicts VAN CL and is inaccurate in critical illness. We compared the Schwartz prediction to the Schwartz-CysC (CysC) equation in critically ill children.

Methods. Children 2-18 years of age receiving intravenous VAN in the Children’s Hospital of Philadelphia PICU were enrolled. Three PK samples were collected during a single steady-state dosing interval in addition to VAN concentrations collected for clinical care. A sample was obtained prior to and during PK sampling for the measurement of CysC and CR. VAN concentrations, dosing histories, and covariates (age, weight, height, sex, eGFR) were analyzed using nonlinear mixed-effects modeling with NONMEM v7.4. Model evaluation/selection was based on successful convergence, precision of the parameter estimates, the Akaike Information Criteria (AIC), and comparison of goodness-of-fit diagnostic plots of models including Schwartz and other published CR and CysC-based GFR-estimating equations that incorporate the novel biomarker cystatin C (CysC) in a population pharmacokinetic (PK) model of VAN CL in critically ill children.

Results. We enrolled 20 subjects age 12.7 years (range: 3.9–18.2); six were female. Median VAN dosing at PK sampling was 57.4 mg/kg/day (range: 26.4–80.1). Median Cr was 83.5 mg/dL (IQR 0.3–0.5) and CysC was 0.5 mg/mL (IQR 0.4–0.8); correlation between Cr and CysC was poor (0.24). Population PK data were described by a two-compartment model with allometric scaling for all parameters. The full age spectrum equation using both Cr and CysC ($\text{eGFR} = 107.3(\text{Cr}/Q)^{0.5} + \text{CysC}/Q_{\text{CysC}}^{0.5}$; Q and $Q_{\text{CysC}}$ were normal values for age) as a covariate on CL had the best fit to the published Cr-CysC equation (AIC = 219.7) and was lower than the Schwartz-CysC model (AIC = 226.6) as the best model fit. Typical population PK parameters (95% CI) normalized to 70 kg were 0.13 L/min (0.11,0.14), 24.5 L (7.7,41.5), and 0.14 L/min (0.01,0.28) for CL, V, and Q, respectively.
1404. A Pharmacokinetic Study on CMS and Colistin and Its Impact on Clinical Cure and Acute Kidney Injury in Critically Ill Patients with Normal Renal Function from South India
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Background. Colistin has re-emerged as last line antimicrobial to combat MDR GNB. There is need for robust pharmacokinetic (PK) and pharmacodynamics (PD) data to guide dosing. This study assessed the PK of CMS and colistin and its impact on clinical cure (CC) and acute kidney injury (AKI) in critically ill patients with normal baseline renal function.

Methods. Adult critically ill patients with colistin susceptible MDR/XDR infections and normal renal function who were treated with intravenous CMS (9MU CMS loading dose (LD)) followed by maintenance (MD) 3MU every 8 hour starting 24 hours after LD were recruited into this prospective observational study. For PK sampling, 3ml venous blood was drawn immediately before LD and at 0.5, 1, 2, 4 and 12 hours after LD. During MD, samples were collected before and at 1, 2 and 8 hours after the ninth and infusion. Colistin plasma concentrations were determined by LC–MS. Results. A total of 280 serum samples were analyzed from 20 patients. Sixty percent had pneumonia. Predominant pathogens were Klebsiella pneumonia (12) and Acinetobacter spp. (8). Mean creatinine clearance (CrCl) was 115 ± 24 mL/minute (72.3–208.8). All patients received combination therapy with colistin, 10% received meropenem and 5(25%) received ticarcillin. Clinical cure rate was 50% (10/20) and mortality rate was 25% (5/20). Mean LD colistin Cmax were 3 ± 1.1 mg/L (1.75–5.14) and 2.37 ± 1.2 mg/L (1.52–5.54) among CC and CF groups, respectively (P = 0.13). MD colistin Css avg was 2.25 ± 1.3 mg/L and 7.8 ± 3.6 mg/L in CC and CF groups, respectively. The mean AUC0-48h/MIC ratio of MD colistin was 92.76 ± 65.76 and 51.8 for CC and CF groups, respectively (P = 0.27). In pneumonia, AUC0-48h/MIC for Acinetobacter spp. was higher in the CC (71.18 ± 10.20) than in the CF group (40.88 ± 16.28) (P = 0.055). Renal injury was mild and 40% at end of therapy. Ten to 20% of patients with CrCl<100 mL/minute had Cmax ≥ 2 mg/L. Majority of CF with AKI had Cmax between 1 and 1.5 mg/L.

Conclusion. Clinical cure was low at 50%. Sub-inhibitory Cas avg and increased volume of distribution following MD could have contributed to high failure. Colistin exposures were similar to those reported in other published cohorts with no consistent exposure-response relationship. Based on these results, there is an important role for therapeutic drug monitoring with Colistin.

Disclosures. All authors: No reported disclosures.