1570. Association Between Vancomycin Area Under the Curve (AUC) and Nephrotoxicity
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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. It is unclear whether increased vancomycin area under the curve (AUC) contributes to acute kidney injury (AKI) risk.

Methods. This retrospective cohort study was undertaken to determine whether vancomycin AUC > 550 is associated with a higher rate of AKI than an AUC < 550. Patients treated with vancomycin for at least 4 days at the St. Louis VA from 1/1/2016 - 9/31/2018 were included. The primary outcome was AKI (defined as an increase in serum creatinine by 0.3 mg/dL or 50% from baseline). Secondary outcomes included length of stay, readmission, or mortality in 30 days, AKI rate with concurrent antibiotics, and AKI rate with comorbidities. The AUC was calculated as daily dose (in mg) divided by vancomycin clearance. The variables of age ≥ 70, vancomycin AUC ≥ 550, creatinine clearance (CrCl) < 50 mL/minute, concomitant antibiotic administration, vancomycin treatment ≥ 7 days, and the presence of comorbidities were included in a bivariate analysis. Variables with a P-value of <0.2 were included in a multivariate logistic regression model.

Results. Two hundred patients were included in the analysis; 100 patients with an AUC ≥ 550, and 100 with an AUC < 550. Only mean vancomycin dose (1722.50 mg vs. 2361.25 mg; P = 0.05), mean AUC (465.88 vs. 696.45; P < 0.05), and peak SCR (1.22 mg/dL vs. 1.48 mg/dL; P = 0.015) were significantly different between groups; AUC < 550 vs. AUC ≥ 550, respectively. Acute kidney injury occurred in 22% (44/200) of all patients; 42% (42/100) with a calculated AUC ≥ 550 developed AKI compared with 2% (2/100) of patients with an AUC < 550 (P < 0.05). The secondary outcomes of concomitant nephrotoxic agents, length of stay, readmission at 30 days, and 30-day mortality were not significantly different between groups. Only age ≥ 70, vancomycin AUC ≥ 550, CrCl < 50 mL/minute, concomitant piperacillin–tazobactam administration, and the presence of comorbidities were included in the multivariate regression. Age ≥ 70, CrCl < 50 mL/minute, and AUC ≥ 550 (OR 49.5; 95% CI 10.1 – 242.3, P = 0.005) were found to be independently associated with risk for developing AKI.

Conclusion. Patients with a calculated vancomycin AUC ≥ 550 were found to have a significantly higher rate of AKI compared with those with an AUC < 550.

Disclosures. All authors: No reported disclosures.

1571. Evaluation of a Single Post First Dose Vancomycin Level to Achieve a Goal Vancomycin AUC
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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. The 24-hour area under the serum concentration–time curve (AUC24) is the most defensible measure to predict the effectiveness and toxicity of vancomycin. The optimize bideed and modified AUC24 was used to adjust and optimize AUC24, however, have yet to be determined. Measuring a trough concentration at steady state has been the traditional method of monitoring vancomycin, but trough is unreliable at estimating AUC24. More accurate methods for estimating AUC24 are paired sample analysis, or a single optimally timed sample combined with population pharmacokinetics. We wished to optimize AUC24 prior to steady state for earlier goal attainment, thereby decreasing risk of treatment failure, resistance, and/or nephrotoxicity. A single optimally timed single post first dose level may be used to estimate drug clearance and thereby AUC. Based on the post first dose concentration and a

population pharmacokinetic model, clearance is calculated, and the dosing regimen can be adjusted to achieve a desired AUC24. Our institution has enabled pharmacist to obtain post first dose vancomycin levels and make early dose adjustments. The aim of this project is to monitor the accuracy of this method and the outcomes of patients who have received post first dose vancomycin levels and subsequent dose assessment/adjustment.

Methods. Single-center cohort study via electronic chart review of patients with vancomycin therapeutic dose monitoring based on post first dose vancomycin levels obtained between January 2019 and April 2019.

Results. 41 patients were dosed and monitored based on post first dose vancomycin levels. Fourteen patients (34%) required dose adjustments based on the post first dose level. Accuracy of assessment was determined in 15 patients (37%) via a steady-state level used to measure vancomycin clearance and AUC24. At steady-state following dose assessment 14/15 (93%) patients had desired targeted goal AUC24. Only two patients (5%) had greater than a 50% increase in baseline serum creatinine.

Conclusion. Post first dose-level analysis resulted in dose regimen modifications in one-third of patients. This consistently allowed the attainment of goal AUC24 at steady-state.

Disclosures. All authors: No reported disclosures.

1572. Evaluation of Vancomycin Levels Following Weight-Based Pre-operative and Re-warming Vancomycin Dosing in Cardiac Surgery
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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. Weight-based dosing of vancomycin in the pre-operative setting is standard practice at our institution based on the 2013 Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery. Our antimicrobial subcommittee recommended a weight-based dosing (15 mg/kg/dose) approach to vancomycin dose during rewarming in cases requiring cardiopulmonary bypass (CPB). However, after discussion with all perioperative stakeholders, administration of vancomycin 1 g intravenously for all patients on CPB at rewarming continued. The aim of this study was to determine whether subsequent rewarming vancomycin doses contributed to the development of postoperative acute kidney injury (AKI).

Methods. This was a prospective cohort study of all cardiac surgery patients undergoing surgery from April 16, 2018 through April 27, 2018 for the development of AKI as defined by RIFLE criteria. Institutional guidelines recommend vancomycin as perioperative prophylaxis in all cardiac surgery cases with a preoperative 15 mg/kg dose, a 1 g rewarming dose, and nomogram-based post-operative dosing. Vancomycin troughs were obtained prior to the first post-operative dose in the intensive care unit. Serum creatinine was recorded on the post-op day (POD) 0, POD 1, and POD 7.

Results. Data were collected on 54 patients over a 2-week period. The median age was 64 years of age, with 41 (76%) male patients. Seven patients (13%) had a prior diagnosis of chronic kidney disease (CKD). Post-op AKI developed in 8 patients (15%) by POD 7; two of which had CKD at baseline. All patients received appropriate preoperative and postoperative dosing. Forty-nine (91%) patients had trough levels obtained, with the median trough 7.6 μg/mL (range 2 – 15.9 μg/mL) prior to the first nomogram-based post-operative vancomycin dose. Higher rates of AKI were associated with a longer duration of CPB rather than vancomycin levels obtained.

Conclusion. The current practice of redosing 1 g vancomycin at rewarming did not appear to contribute higher rates of AKI. In addition, all vancomycin trough levels reviewed were less than 20 μg/mL. Levels observed in this study are lower than previously described in the literature to cause nephrotoxicity. Further evaluation of vancomycin use in this setting is warranted.

Disclosures. All authors: No reported disclosures.

1573. Population Pharmacokinetic Analyses for Cefepime in Adult and Pediatric Patients
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Session: 162. PK/PD and Susceptibility Testing
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Background. Cefepime (CEF) is commonly used for adult and pediatric infections. Several studies have examined CEF's pharmacokinetics (PK) in various populations; however, a unifying PK model for adult and pediatric subjects does not yet exist. We developed a combined population model for adult and pediatric patients and validated the model.

Disclosures. All authors: No reported disclosures.
Methods. The initial model includes adult and pediatric patients with a rich cetepine sampling design. All adults received 2 g CEF while pediatric subjects received a mean of 49 (SD 5) mg/kg. One- and two-compartment models were considered as base models and were using a non-parametric adaptive grid algorithm within the Pmetrics package 1.5.2 (Los Angeles, CA) for R 3.5.1. Compartamental model selection was based on Akaike information criteria (AIC). Covariate relationships with PK parameters were visually inspected and mathematically assessed. Predictive performance was evaluated using bias and imprecision of the population and individual predictions. External validation was conducted using a separate adult cohort.

Results. A total of 45 subjects (n = 9 adults; n = 36 pediatrics) were included in the initial PK model build and 12 subjects in the external validation cohort. Overall, the data were best described using a two-compartment model with volume of distribution (V) normalized to total body weight (TBW/70 kg) and an allometric scaled elimination constant (Ke) for pediatric subjects (AIC = 4,138.36). Final model observed vs. predicted plots demonstrated good fit (population R² = 0.87, individual R² = 0.69). Figure 1a and b. For the final model, the population median parameter values (95% credibility interval) were V0 (total volume of distribution), 11.7 ± 10.2–14.6; Ke for adult, 0.66 hour⁻¹ (0.38–0.78); Ke for pediatric, 0.82 hour⁻¹ (0.64–0.85); KCP (rate constant from central to peripheral compartment), 1.4 hour⁻¹ (1.3–1.8); KPC (rate constant from peripheral to central compartment), 1.6 hour⁻¹ (1.2–1.8). The validation cohort has 12 subjects, and the final model fit the data well (individual R² = 0.75).

Conclusion. In this diverse group of adults and pediatrics, a two-compartment model described CEF PK well and was externally validated with a unique cohort. This model can serve as a population prior for real-time PK software algorithms.

1574. Predictive Ability and Bias of Vancomycin Population PK Models in an Obese Adult Population
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Background. Accurate dosing of vancomycin is difficult due to high inter-individual variability of vancomycin pharmacokinetics (PK), and is particularly challenging in obese patients. Vancomycin is hydrophilic, yet total body weight (TBW) has traditionally been used for dosing in the general population, and also into the obese population. The aim of this study was to evaluate the performance of published vancomycin PK models in a large set of routine clinical data obtained from an obese population.

Methods. De-identified data were available from 1717 courses of vancomycin administered to obese adults (BMI ≥ 30) from hospitals across the United States, EU, and Australia. Three population PK models, Buelga et al. (2005), Goti et al. (2018), and an obese-specific model, Adane et al. (2015), were used to predict plasma concentrations at the time of each administration. Using ideal body weight (IBW) on Vd and no correction for weight on CL provided the best fit. The derived model accounted for 81% of variance in plasma concentration and exhibited negligible bias by obesity class (population MME = -0.75 (i), -0.06 (ii), and -0.50 (iii) mg/L; individual MME = -0.20 (i), -0.02 (ii), and -0.02 (ii) mg/L).

Conclusion. Existing vancomycin population PK models for use in the obese population are biased in higher obesity classes due to the use of total body weight. A novel population PK model developed using ideal body weight exhibits negligible bias across obesity classes as well as improved predictive ability.

Disclosures. All authors: No reported disclosures.

1575. Vancomycin Loading Doses and Nephrotoxicity on Medicine Teaching Services
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Session: 162. PK/PD and Susceptibility Testing
Friday, October 4, 2019: 12:15 PM

Background. IDSA guidelines recommend the usage of a loading dose when using vancomycin for seriously ill patients to rapidly achieve adequate trough concentrations. While the relationship between vancomycin and nephrotoxicity is the focus of many studies, and with the strength of that relationship still debated, few studies have examined the relationship between vancomycin loading doses and nephrotoxicity.

Methods. We performed a retrospective cohort study examining vancomycin dosing for internal medicine teaching services’ patients over the 2014–2015 academic year at one academic medical center. We generated a list of all hospitalized patients aged 18–85 who received vancomycin and were admitted to a teaching service. Patient data were extracted from the inpatient EMR via manual chart review. Patients were excluded if their pretreatment calculated glomerular filtration rate (GFR) was less than 50 mL/minute, if they received less than three doses of vancomycin, or if their initial dose was subtherapeutic (<10 mg/kg). Nephrotoxicity was determined by 7-day acute kidney injury (AKI) rate. Patients in the loading dose (>20 mg/kg) cohort were compared with those in the standard dose cohort (10–20 mg/kg). Our primary modeling used multi-variable logistic regression with AKI as our outcome of interest.

Results. 438 of the initial 804 patients were enrolled. The loading dose (n = 365, 83%) and standard dose (n = 73, 17%) cohorts were not significantly different regarding demographics, GFR, nephrotoxic drug exposure, total vancomycin received, trough levels, or comorbidities, and were only significantly different regarding body mass index (BMI). The 7-day AKI rate was not significantly different between the two arms (6.3% in the standard dose arm and 8.2% in the loading dose arm P = 0.6). AKI rate significantly increased in both arms in the setting of concurrent piperacillin–tazobactam and vancomycin administration (OR 2.5, P = 0.04). There was no association between BMI and AKI.

Conclusion. Few studies have examined the relationship between nephrotoxicity and vancomycin loading doses. The results of this study provide evidence that the use of loading doses is not significantly associated with increased 7-day AKI rate.

Disclosures. All authors: No reported disclosures.

1576. Delaying the Start of Maintenance Vancomycin After a Loading Dose to Avoid a High 0–24h AUC
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Session: 162. PK/PD and Susceptibility Testing
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Methods. In a retrospective chart review of patients admitted to our hospital, we noted that many physicians wait up to 12 hours after a loading dose to start maintenance vancomycin. We hypothesized that this delay was to avoid a high 0–24h AUC.

Results. 438 of the initial 804 patients were enrolled. The loading dose (n = 365, 83%) and standard dose (n = 73, 17%) cohorts were not significantly different regarding demographics, GFR, nephrotoxic drug exposure, total vancomycin received, trough levels, or comorbidities, and were only significantly different regarding body mass index (BMI). The 7-day AKI rate was not significantly different between the two arms (6.3% in the standard dose arm and 8.2% in the loading dose arm P = 0.6). AKI rate significantly increased in both arms in the setting of concurrent piperacillin–tazobactam and vancomycin administration (OR 2.5, P = 0.04). There was no association between BMI and AKI.

Conclusion. Few studies have examined the relationship between nephrotoxicity and vancomycin loading doses. The results of this study provide evidence that the use of loading doses is not significantly associated with increased 7-day AKI rate.

Disclosures. All authors: No reported disclosures.