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Case Report

Eight unexpected cases of vancomycin associated acute kidney injury with contemporary dosing

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ABSTRACT

Vancomycin is one of the most commonly utilized antibiotics in US hospitals. It remains the drug of choice for the treatment of serious infections caused by methicillin-resistant *Staphylococcus aureus*. For many of these deep-seated infections, guidelines recommend achieving troughs of 15–20 mg/L for treatment efficacy. At our institution we observed a number of cases of presumed vancomycin-induced acute tubular necrosis clinically diagnosed by the nephrology service. We report eight cases of presumed vancomycin-induced acute tubular necrosis, three of which required hemodialysis before resolution of nephrotoxicity. Only three of the eight patients received nephrotoxins prior to development of nephrotoxicity. All eight patients ultimately recovered renal function following discontinuation.

1. Introduction

Vancomycin is one of the most commonly utilized antibiotics in hospitals [1–3]. It remains the drug of choice for serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and is recommended as part of an empiric regimen in a number of common infections [4]. As resistant strains with rising minimum inhibitory concentrations (MICs) are increasingly common, aggressive dosing of vancomycin for the treatment of deep seated MRSA infections is becoming commonplace. Current guidelines for the treatment of MRSA recommend goal troughs of 15–20 mg/L for pneumonia, central nervous system infections and endocarditis [5]. These increasing vancomycin exposures have given rise to concerns of increased nephrotoxicity.

While nephrotoxicity was originally attributed to the impurities of the initial formulations, recent data have suggested that contemporary formulations of vancomycin may be nephrotoxic, even as monotherapy [6–9]. Now, with increasing daily doses being required for the optimal treatment of many infections, clinical studies have sought to describe those at highest risk for developing vancomycin-induced nephrotoxicity [7,8,10–14]. Meta-analyses and observational studies have identified a number of risk factors associated with developing vancomycin induced nephrotoxicity. Some of these risk factors include concurrent nephrotoxins, total daily doses ≥4 g, troughs ≥15 mg/L and prolonged courses of therapy [7,8,11,13].

Despite over 60 years of experience in using this antibiotic, the mechanism of vancomycin-induced nephrotoxicity is not fully understood. Vancomycin-induced acute interstitial nephritis (AIN) has been described and is primarily attributed to allergic mechanisms. More controversy exists over whether vancomycin alone can cause acute tubular necrosis (ATN). It has been suggested that vancomycin causes direct injury to the proximal tubules in the kidney via oxidative stress [15–18]. Although the exact mechanism has not been defined, either maximal serum vancomycin concentrations or first 24- hour area under the concentration time curve appear to drive the severity of the injury [19]. Herein we describe eight cases of severe vancomycin-induced ATN clinically diagnosed by the nephrology consult service at our institution.

2. Case reports

Cases were identified between July of 2009 and May of 2011 at Northwestern Memorial Hospital (NMH), an 897-bed tertiary

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hospital in Chicago, IL (see Table 1). Notably at our institution, only 1 or 2 g aliquots of vancomycin were utilized during this time period. Vancomycin doses were determined by the primary team, with follow up concentration monitoring and dosage adjustment by pharmacists as appropriate. Cases were classified as having an acute kidney injury (AKI) event associated with vancomycin exposure if the individual in question had an increase in serum creatinine (SCr) > 0.5 mg/dL, ≥ 50% increase in SCr over baseline, or a 50% decrease in creatinine clearance (CrCl) from baseline while receiving intravenous vancomycin therapy in the absence of an alternative explanation [20]. Recovery of renal function was defined as a measure of SCr within 150% of baseline, a decrease of SCr to within 0.5 mg/dL of baseline or a recovery of CrCl to within 50% of baseline. The determination of ATN as the primary focus of nephrotoxicity was made by the nephrology consult service. Patient characteristics, infection sites and vancomycin dose and intervals were collected. Additionally, medication administration records were searched for any preceding or concurrent nephrotoxins. Clinical laboratory values from serum and urine chemistries were also collected. This study was approved by the Institutional Review Board at Midwestern University and Northwestern University.

Patient specific vancomycin exposures were determined using BestDose version 1.126 (Laboratory of Applied Pharmacokinetics, Los Angeles, CA). This program utilized patient specific covariates (i.e. CrCl and weight), exact vancomycin doses and times delivered, and measured vancomycin concentrations to identify the most likely vancomycin exposure profile. The most likely exposure profile was defined as the weighted average concentrations based on the observed data and the Bayesian priors. Exposure metrics (i.e. AUC, C_{max} and C_{min}) were calculated for each patient according to their first 24-h exposure to vancomycin for the regimen that preceded acute kidney injury. The area under the curve (AUC) is presented as the AUC in the first 24 h of exposure (as this exposure is the least likely in the causal pathway of kidney damage) [19,21]. C_{max} is the maximal predicted concentration, and C_{min} is the trough within the first 24 h. For patients who were discharged on vancomycin and readmitted with AKI, only the first 24-h inpatient exposure was estimated as relevant outpatient data were not available.

2.1. Case 1

A 49-year old female with a history of diabetes mellitus, peripheral artery disease and multiple amputations was transferred to our hospital from an inpatient rehabilitation center for the treatment of a MRSA peripherally inserted central catheter (PICC) line infection. She was started on 1 g of vancomycin (10 mg/kg) every 8 h (q8h). Her baseline SCr was 0.8–1.0 mg/dL. On hospital day 2, her dose was empirically increased to 2 g (20 mg/kg) q8h for 2 doses, then decreased back to 1 g q8h. Her predicted AUC, C_{max} and C_{min} for the first 24 h of therapy were 1584.1 mg*h/L, 112.6 mg/L and 87.2 mg/L, respectively; however, these values indicate that she may have gone into acute kidney failure on day one and an estimate of her vancomycin profile prior to nephrotoxicity is unknown. On hospital day 4, it was noted that her SCr had increased to 1.74 mg/dL. She was not hypotensive at any point leading up to this increase in SCr. Of note, she had received lisinopril twice during this time. On this same day, a random vancomycin serum concentration was obtained revealing a concentration of 95.8 mg/L. The next day she received oral contrast for a chest CT due to concern for a developing pleural effusion. Urine chemistry studies were conducted on hospital day 6, showing a fractional excretion of sodium (FeNa) of 23%, a renal ultrasound this same day showed no evidence of obstruction. Hemodialysis (HD) was started on hospital day 8 per the nephrology service. Her SCr continued to increase and peaked at 4.17 mg/dL on hospital day 17, 13 days after stopping vancomycin. She continued to receive hemodialysis throughout her admission as well as in the outpatient setting. Her SCr continued to trend down, eventually returning to baseline 46 days after stopping vancomycin. Hemodialysis was stopped at this time.

2.2. Case 2

A 53-year-old male presented with C1–C2 osteomyelitis. His past medical history includes hypertension for which he was taking losartan. He was initiated on vancomycin 2 g (15.75 mg/kg) every 12 h (q12h) and piperacillin-tazobactam (TZP). At baseline, his SCr was 1.1 mg/dL. He received intravenous contrast for a head and neck CT on the second day of his hospitalization. He was discharged after 5 days of therapy. In the first 24 h of therapy, his estimated vancomycin exposure was an AUC of 299.5 mg*h/L, C_{max} 41.7 mg/L and C_{min} 1.7 mg/L. Before discharge, his SCr was 1.38 mg/dL, and a vancomycin trough returned a serum concentration of 14.9 mg/L. At discharge, he was transitioned from TZP to ertapenem and given ibuprofen for pain control.

Three days following discharge, the patient presented with new onset abdominal pain, fever and chills. At this time his SCr was noted to be 5.29 mg/dL and a random vancomycin serum concentration revealed a concentration of 93.8 mg/dL. His FeNa on admission was 4.6%, no eosinophils were detected in the urine. Vancomycin was discontinued on readmission. He was not oliguric or hypotensive at any point during the second admission. Upon his second discharge (6 days after stopping vancomycin) his SCr had decreased to 3.19. His abdominal pain and fevers had resolved by this time. Upon outpatient follow-up (46 days after stopping vancomycin) his SCr had returned to 1.48 md/dL.

2.3. Case 3

A 20-year-old female was admitted status post motor vehicle accident. At that time, she received contrast for CT imaging of her head, showing intracranial hemorrhage with midline shift, requiring craniotomy. On hospital day 8, she was started on vancomycin 1 g (16.7 mg/kg) every 12 h and piperacillin-tazobactam for the treatment of suspected ventilator associated pneumonia. She was not hypotensive at the time and was at her baseline SCr of 0.4–0.5 mg/dL. After 4 days of therapy, her vancomycin dose was increased to 1 g every 6 h in response to a vancomycin trough that was undetectable. Another serum concentration was taken after 5 doses on this new regimen, prompting an increase to 2 g (33.3 mg/kg) every 8 h. During the first 24 h of therapy on this dosing scheme, her estimated vancomycin AUC, C_{max} and C_{min} were 644.7 mg*h/L, 90.4 mg/L and 4.6 mg/L, respectively. Of note she received contrast for a CT on day 5 of therapy. On day 9 of therapy (4 days after starting 2 g every 8 h), a vancomycin trough was obtained, showing a serum concentration of 54.9 mg/dL. At this point, her SCr was 2.12 mg/dL and urine chemistries suggested an intrinsic etiology (FeNa = 3.7%) without eosinophiluria. Vancomycin was stopped at this time. Her SCr peaked at 4.19 mg/dL two days after stopping vancomycin. She was not oliguric at any point during her admission. Vancomycin was undetectable at discharge, 15 days following her last dose, additionally her SCr at this time was 1.43 mg/dL. Her SCr returned to baseline 17 days after discharge, 31 days after stopping vancomycin.

2.4. Case 4

A 46-year-old female with a history of metastatic breast cancer, presented with symptoms of a wound infection following a ventriculoperitoneal shunt revision. At baseline, her SCr was