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PATIENT SAFETY NETWORK

Failure to Reevaluate

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The Case

A 61-year-old woman receiving palliative chemotherapy for non–small-cell lung cancer at a community hospital developed methicillin-resistant *staphylococcus aureus* (MRSA) bacteremia and endophthalmitis originating from her port. Vancomycin 1.25 grams intravenously twice daily was initiated, and the patient was transferred to a large academic medical center for ophthalmologic consultation and further treatment. Vancomycin was continued upon transfer until she was found to have a rapidly rising serum creatinine (Scr). The initial Scr was 0.4 mg/dL at the community hospital; it had increased to 0.8 mg/dL on admission to the receiving facility and was apparently interpreted as "normal," since it still fell within "normal" range. The patient was recognized to be in acute renal failure when her creatinine reached 1.09 mg/dL the day after transfer. Notably, the vancomycin trough at this time was 64 mg/L. The vancomycin blood level had not been checked previously throughout her treatment.

As a result of her renal failure, the patient rapidly developed non-anion gap metabolic acidosis and, 5 days after transfer, required urgent dialysis for volume overload and worsening acid-base status. Urine and blood studies failed to identify a clear cause of her renal failure. At present, the patient continues to be anuric and dialysis dependent, and she will likely leave the hospital receiving palliative chemotherapy and a 6-week course of vancomycin. She has a new tunneled catheter for ongoing dialysis treatments.

The Commentary

Acute kidney injury (AKI) is a common condition associated with up to 7% of all hospital admissions, with drug-induced nephrotoxicity accounting for one-third of these cases.(1) Vancomycin is an antibiotic that is being increasingly prescribed in light of the increasing prevalence of invasive infections caused by MRSA in the United States.(2,3)

On first glance, the admitting resident's course of action might appear reasonable based on what was known at the time (a single Scr value) and the assumption that the vancomycin dose given at the outside

hospital was appropriate. In order to safeguard patients against drug-induced toxicity, though, several practice- and systems-related issues highlighted by this case deserve attention.

First, vancomycin is renally eliminated and has a narrow therapeutic index, with potential nephrotoxicity, particularly with concomitant nephrotoxins and with more aggressive dosing. Thus, patients receiving therapy beyond several days require routine monitoring of renal function and serum vancomycin concentrations to maximize efficacy and minimize toxicity, particularly those who have concomitant risk factors for development of nephrotoxicity (i.e., receipt of other nephrotoxins). Scr is commonly measured to assess renal function but may vary with a variety of renal and nonrenal factors such as age, gender, weight, muscle metabolism, and protein intake.(4) Specifically, patients with end-stage liver disease or reduced muscle mass secondary to malnutrition or immobility can exhibit a lower than normal baseline Scr value. As such, those patients experiencing significant renal injury (as demonstrated by significant elevations from baseline, as in this case) may still have "normal" Scr values.

Had the admitting Scr value of 0.8 mg/dL been compared with the patient's lower than normal initial Scr value of 0.4 mg/dL from the outside hospital, the admitting resident would have recognized the doubling and been prompted to order a serum vancomycin trough concentration prior to the next administration of the drug. Alternatively, even patients without significant changes in Scr from baseline may be experiencing nephrotoxicity from vancomycin. In these cases, a vancomycin trough concentration obtained at the time of admission could reveal excessive drug accumulation due to subclinical AKI.

Scr has been recognized as an insensitive and nonspecific marker for detecting AKI, with a change in values often occurring only after significant renal damage. To facilitate early detection of AKI and allow prompt intervention, the Acute Kidney Injury Network has proposed new uniform standards for diagnosing AKI based on abrupt changes in Scr (increase > 0.3 mg/dL in 48 h) or urine output (6 h).(5) In addition, future novel urinary biomarkers (e.g., KIM-1) that are more specific and sensitive than Scr may result in earlier diagnosis of AKI, potentially minimizing toxicity.(6)

Given the challenges in detecting vancomycin toxicity and AKI, a key principle is this: besides monitoring the patient's renal function, the most accurate and practical method to monitor efficacy and toxicity of vancomycin therapy is to obtain serum trough concentration at steady state (just before the fourth dose).(7) Existing literature suggests that vancomycin monotherapy is minimally nephrotoxic. The risk of nephrotoxicity is strongly associated with dose and duration of therapy, compounded by the presence of other risk factors such as concomitant receipt of nephrotoxins or vasopressor therapy and underlying physiologic impairment.(8-10) Recent emergence of MRSA with reduced susceptibility and treatment failure has led to recommendations from published guidelines to dose vancomycin more aggressively, targeting trough concentrations of 15-20 mg/L for complicated infections (e.g., bacteremia, pneumonia, osteomyelitis).(7,11) At the high trough concentration range, the frequency of nephrotoxicity has been reported at 12%-33% in patients with additional risk factors and 2%-8% in the absence of concomitant risks.(8-10,12)

Medication records of patients transferring from outside facilities often do not include detailed therapeutic drug monitoring records. This case highlights the importance of assessing vancomycin therapy through the monitoring of trough levels. In this patient, particularly in light of the higher than usual dose of 1 g and the

likelihood that the patient has received another nephrotoxin (i.e., cisplatin for lung cancer), it is imperative to order a vancomycin serum level with admission labs. Given the trough level of 64 mg/L (well in the supratherapeutic range) the day after transfer, this patient probably had a supratherapeutic level at the time of transfer. Had it been recognized, the admitting resident would have been prompted to reevaluate vancomycin dose or consider alternative antibiotics. Upon development of acute renal failure, vancomycin should be promptly discontinued and alternative agents (i.e., daptomycin) should be prescribed based on organism sensitivity.

Additionally, safeguards can be established at the systems level to minimize drug-induced adverse events. Computerized prescriber order entry systems and/or pharmacy computer systems can prompt for Scr and vancomycin trough values at the time of order entry. Proactive involvement of pharmacists at the time of therapeutic decisions is encouraged, particularly when prescribing drugs with narrow therapeutic index. The participation of pharmacists as active members of physician rounding teams reduces preventable adverse drugs events by 78%, with the most common intervention associated with drug dosage or frequency.(13,14) Other ways of involving pharmacists in antimicrobial dosing include pharmacist-managed dosing protocols for target agents and, more specifically, through active involvement in antimicrobial stewardship programs.

Take-Home Points

This patient's experience illustrates several key patient safety points specific to prescribing potentially nephrotoxic and/or renally eliminated drugs (e.g., vancomycin):

- Patients transferred from an outside facility receiving a narrow-therapeutic-index, renally eliminated drug should have baseline renal function and serum drug levels drawn. These levels should be routinely followed during the entire course of therapy.
- Scr may not reflect renal function in patients with reduced muscle mass, malnutrition, and end-stage liver disease. Interpretation of Scr value should be made in the context of the patient's clinical condition and relative to a baseline value.
- Consultation with a pharmacist is encouraged when dosing a narrow-therapeutic-index drug, particularly if therapeutic drug monitoring is required.

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