Acute Renal Failure Owing to Inadvertent Vancomycin Overdose

Vancomycin Removal by Continuous Arteriovenous Hemofiltration

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ABSTRACT

Acute renal failure developed in a patient who received 56 grams of vancomycin intravenously over a 10 day period. The resulting serum vancomycin level was 284 μg per ml and declined to 140 μg per ml in a linear fashion with the institution of continuous arteriovenous hemofiltration (CAVH). Our conclusion is that high blood vancomycin levels may be nephrotoxic and CAVH may be an effective means of vancomycin removal in patients with acute renal failure.

Introduction

Vancomycin is a cell-wall active antibiotic with significant bactericidal activity against gram-positive bacteria. Its use in the treatment of infections with Staphylococcus aureus and Staphylococcus epidermidis has increased with the growing frequency of isolates demonstrating methicillin-resistance.3,6 Early reports of nephrotoxicity owing to vancomycin were attributed to impurities in the preparations available at that time. Appel et al recently reviewed the evidence for vancomycin nephrotoxicity in animals and humans and concluded that the antibiotic has a low potential for renal damage when used alone.2 Studies which reported an increased risk of nephrotoxicity are complicated by the concomitant use of other nephrotoxic drugs, in particular aminoglycosides, or the presence of other clinical disease states known to be associated with a high risk of acute renal failure.5,9,10 A case is reported of acute renal failure which is believed to have been induced by the inadvertant administration of toxic quantities of vancomycin, resulting in the highest serum level documented thus far in the literature. The vancomycin was readily removed by continuous arteriovenous hemofiltration (CAVH).

Case Report

A 54-year-old white male was hospitalized with recurrent headaches, nausea, and vomiting. His past medical history was notable for a thalamotomy for Parkinson's disease 20 years earlier and normal pressure hydrocephalus treated with bilateral ventriculoperitoneal shunts 22 months earlier. On admission he was noted to have nuchal rigidity. Cultures of cerebrospinal fluid from the unilaterally functioning left shunt grew S. epidermidis. He was initially placed on
two grams of cefotaxime intravenously every four hours. When the patient failed to improve, he was transferred to the Portland Veterans Administration Medical Center where removal of both ventriculoperitoneal shunts and ventriculostomy placement were performed. A contrast-enhanced computerized tomography scan prior to surgery showed a small left occipital low density area but no abscess. Cultures of blood and urine were negative; cerebrospinal fluid cultures again grew *S. epidermidis*. Cefotaxime was discontinued and 1 gram of vancomycin intravenously every four hours was administered.

The patient improved initially but continued to require intravenous fluids because of persistent nausea. On the 11th hospital day, oliguria was noted (200 cc per 24 hours) despite adequate hydration. Serum creatinine had risen from 0.7 mg per dl on admission to 7.7 mg per dl. In addition to the 56 grams of vancomycin administered to that point, medications included sinemet, hydroxyzine, meperidine, acetaminophen, metoclopramide, triazolam, and docu­sate. There was no prior history of renal insufficiency, urinary tract infections, hypertension, diabetes, or analgesic abuse.

Physical examination revealed an emaciated male with a temperature of 37.3° C, blood pressure of 130/72, and a pulse of 64 beats per minute. There were no postural blood pressure changes noted. The chest and cardiac examinations were unremarkable except for the presence of a previously noted grade II/VI systolic ejection murmur. The abdomen was distended with rare bowel sounds. There was no masses, tenderness, or costovertebral angle tenderness elicited. A trace of pedal edema was noted. Neurological exam revealed confusion and diffuse myoclonus.

Laboratory examination showed a sodium of 127 mEq per l; potassium, 6.2 mEq per l; chloride, 93 mEq per l; bicarbonate, 17 mM per l; BUN, 36 mg per dl, and creatinine, 7.6 mg per dl. The urine sediment, obtained after placement of a Foley catheter, showed a specific gravity of 1.010 with protein 3+, 0 to 3 WBC/HPF, many RBC/HPF, and occasional granular casts.

The patient was suspected of having acute renal failure owing to an overdose of vancomycin. Following unsuccessful attempts to increase urine flow with low-dose intravenous dopamine and furosemide, femoral arterial and venous cannulas were placed for CAVH, necessitated by the daily administration of large volumes of intravenous hyperalimentation fluid. A vancomycin level was then found to be 284 μg per ml. The patient’s subsequent renal replacement therapy and renal course, as well as the decline in the serum vancomycin levels, are shown in figures 1 and 2. Vancomycin serum levels showed a linear decline during CAVH (figure 2). Urine output increased on the 36th hospital day, and renal function gradually improved.

**Discussion**

This patient developed acute renal failure in the setting of inadvertant administration of one gram of vancomycin every four hours associated with a serum vancomycin level of 284 μg per ml. In the absence of a renal biopsy, shunt nephritis or other causes of acute renal failure cannot definitively be excluded. Likewise, the absence of any measurements of renal function between the time of the admission, the contrast-enhanced computerized tomography scan, and the elevated BUN and creatinine noted seven days later does not exclude contrast nephropathy as a cause of this patient’s acute renal failure. Nevertheless, the extremely high serum vancomycin levels and the patient’s clinical course seem more consistent with vancomycin-induced acute renal failure. The resolution of the acute renal failure, and at least some of the neurologic abnormalities (myoclonus) which were temporally related with the significant decline in serum vancomycin levels, supports the case for vancomycin nephrotoxicity.

While the risk of toxicity may be reduced with the more chemically pure formulations of vancomycin, a potential for renal damage may be present if inappropriately high doses are administered. In addition, vancomycin has been reported to cause acute interstitial nephritis.

The rapid decline in serum vancomycin levels noted during CAVH is of interest. Vancomycin is poorly removed by conventional hemodialysis and peritoneal dialysis because of its large molecular weight of 1448 daltons, although drug removal may be substantially augmented by resin or charcoal hemoperfusion. Based on previous pharmacokinetic data that showed negligible extrarenal clearance of vancomycin and almost no tubular secretion or reabsorption, a nomogram for vancomycin dosage adjustment in patients with decreased renal function based on creatinine clearance has been developed.
Thus far, there have been no reports on the use of CAVH in patients with high serum vancomycin levels and suspected nephrotoxicity. The sieving coefficient for the drug during CAVH is known and suggested to us that significant drug removal would occur with this therapy when drug levels are high. This was borne out as demonstrated in figure 2.

Although pharmacokinetic parameters were not directly measured, the estimated $T_{1/2}$ during CAVH of approximately 4.9 days was appreciably less than that observed after discontinuation of CAVH. This was approximately 10.9 days. This latter half-life is consistent with data reported for vancomycin elimination in anephric subjects and suggests that drug removal was negligible during standard hemodialysis. Based on an assumed protein binding of 10 percent, a sieving coefficient of 90 percent, and an average ultrafiltration rate of 9.6 liters per day during CAVH, a predicted drug removal of 9.1 grams of vancomycin was achieved during the five days of CAVH. This figure is probably an overestimate of true hemofiltration drug removal as Noonan et al have demonstrated substantial nonrenal clearance of vancomycin which is concentration dependent,
increasing with higher steady-state vancomycin levels.\textsuperscript{7}

In summary, it is believed by the present authors that this patient developed acute renal failure secondary to the inadvertent administration of excessive vancomycin associated with very high serum levels. Our case suggests that CAVH may be of benefit not only in the management of acute renal failure, but also in the removal of vancomycin from the blood. Resin hemoperfusion is an alternative to CAVH for vancomycin removal.\textsuperscript{1}

References