Open Forum Infectious Diseases

BRIEF REPORT

Acute Tubular Necrosis Associated With High Serum Vancomycin and Tobramycin Levels After Revision of Total Knee Arthroplasty With Antibiotic-Containing Calcium Sulfate Beads

Adrienne H. Ma,[1] Courtney Hoffman,[2] and John I. Mcneil[3]

[1]Department of Pharmacy, The George Washington University Hospital, Washington, DC; [2]Department of Pharmacy, MedStar Montgomery Medical Center, Olney, Maryland; [3]Infectious Disease Medicine, Silver Spring, Maryland

We present the case of a 59-year-old male who developed acute tubular necrosis with a serum tobramycin level of 15.9 mg/L after instillation of tobramycin and vancomycin calcium sulfate beads for infected total knee arthroplasty. We emphasize standardizing surgical protocols to mitigate nephrotoxicity based on current efficacy and safety data.

Keywords. acute tubular necrosis; calcium sulfate beads; tobramycin; total knee arthroplasty; vancomycin.

CASE REPORT

A 59-year-old male presented to the emergency department with onset of left knee pain and chills. He reported incurring a knee abrasion 1 week prior while installing hardwood floors at work. His medical history was significant for ankylosing spondylitis on long-term adalimumab, deep vein thrombosis of the left lower extremity, uveitis, and total left knee replacement in 2013 with the Biomet Vanguard total knee arthroplasty system. He also had a methicillin-sensitive *Staphylococcus aureus* (MSSA) left knee infection in 2014 treated with successful irrigation and debridement (I&D) with polyethylene exchange. Physical examination noted warmth, swelling, and abrasion on the left knee, whereas radiology showed left knee effusion.

On admission, her white blood cell count (WBC) was 18.9 cells/mm^3, with a normal serum creatinine (SCr) of 1.13 mg/dL. Her blood pressure and respiratory rate were normal. The patient (weight 78.6 kg) was then started on parenteral ceftriaxone and vancomycin, which were changed to cefepime and vancomycin after infectious disease consultation. Orthopedic surgical consult determined likely infected left total knee arthroplasty. Subsequent aspiration of the left knee showed a WBC of 27 240 cells/mm^3. Her vancomycin level before surgery was 13.4 mcg/mL, and the dose had been increased from 1.25 g every 12 hours to 1.5 g every 12 hours, per pharmacy protocol, to achieve a goal of 15–20 mcg/mL. The patient was then taken to the operating room for I&D with polyethylene exchange. A batch of calcium sulfate Stimulan beads comprised of 1 g of vancomycin and 2.4 g of tobramycin was made. A mix of 3-mm and 4.8-mm beads was packed into the gutters and suprapatellar area of the knee (total final amount used was unconfirmed). This method should produce beads with approximately 3.9–4.13 mg of vancomycin and/or 1.02 mg of tobramycin [1, 2].

The patient met KDIGO criteria for acute kidney injury by postoperative day (POD) 1 [3]. Nephrology was then consulted, and the patient was diagnosed with likely acute tubular necrosis presumed from acute tobramycin toxicity. Renal ultrasound did not show any significant abnormalities. The patient described decreased urine output. SCr peaked on POD5 at 8.28 mg/dL without need for dialysis. Calcium levels were also transiently elevated. Trends in relevant blood values are described in Table 1. Vancomycin levels were 40.9 and 37.4 mcg/mL on POD1 and POD2, whereas tobramycin levels were 15.9 on POD2 but were still significantly above normal trough levels at 5.0 mcg/mL on POD5. Goal gentamicin levels are typically <1 mcg/mL for urinary tract infection/pyelonephritis and gram-positive synergy and <2 mcg/mL for severe or life-threatening gram-negative infections.

Final culture results showed MSSA infection in the synovial fluid and wound. The patient was deescalated to nafcillin and discharged on parenteral cefazolin on POD8 with orders for close follow-up at the infectious diseases clinic. At discharge, the patient had recovered full urine output.

DISCUSSION

Although prosthetic joint implantation remains an effective quality of life intervention, the rare consequence of prosthetic joint infection (PJI) is difficult to treat and requires the need for subsequent surgical intervention such as local I&D with implant retention and 1-stage and 2-stage exchanges. The use of antibiotic-impregnated bone cement spacers and parenteral antibiotics is considered standard for treatment of chronic PJI, but the role of antibiotic-loaded calcium sulfate beads for the treatment of prosthetic joint infection is less well defined [4, 5]. The Infectious Diseases Society of America (IDSA) guidelines for PJI recommend spacers in both 1- and 2-stage exchanges, followed by a 2- to 6-week pathogen-specific intravenous or highly bioavailable oral antimicrobial therapy. However, some

Received 19 January 2019; editorial decision 7 March 2019; accepted 8 April 2019.

Correspondence: A. H. Ma, PharmD, Department of Pharmacy, The George Washington University Hospital, 900 23rd Street NW, Washington, DC 20037 (adrienne.ma@gwu-hospital.com).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofz141

Table 1. Relevant Bloodwork Results

Lab Parameter	Reference Range	On Admission (10/15)	Day of Surgery (10/17)	POD1 (10/18)	POD2 (10/19)	POD3 (10/20)	POD4 (10/21)	POD5 (10/22)	POD6 (10/23)
Complete blood count									
White cell count, cells/mm^3	4.8–10.8 × 10^3	18.9	15.63	10.09	10.30	8.25	10.9	—	—
Basic metabolic panel									
BUN, mg/dL	9.0–20	12	16	22	34	47	55	56	62
Creatinine, mg/dL	0.67–1.17	1.13	1.19	2.64	5.21	6.51	7.81	8.28	7.99
Calcium, mg/dL	8.4–10.2	8.4	8.3	9	9.2	10.2	10.9	10.7	10.4
Albumin	3.5–5.0							2.1	
Corrected calcium, mg/dL		9.92	9.82	10.52	11.12	11.72	12.42	12.22	11.92
Phos, mg/dL	2.5–4.5							5.5	
C-reactive protein, mg/L	<3.0	75.6							
Antibiotic serum levels									
Tobramycin, mg/L	<2				15.9		6.4	5.0	
Vancomycin, mcg/mL	10–20		13.4	40.9	37.4				

Abbreviation: BUN, blood urea nitrogen; POD, postoperative day.

members of the IDSA panel also caution against the use of spacers for MRSA-PJIs, small-colony variants, or fungal PJIs.

Historically, polymethylmethacrylate (PMMA) and purified calcium sulfate from gypsum have served as imperfect vehicles to deliver local antibiotics. PMMA beads are nondissolvable and may develop biofilm formations with prolonged implantation time, requiring additional intervention to remove beads after treatment. Gypsum-derived calcium sulfate beads are problematic, as they often contain byproduct impurities that provoke inflammation and subsequent impaired wound healing and increased drainage. As a result, various types of improved biosynthetic manufacturing of pure calcium sulfate have become popular, including brands such as Stimulan, Herafill, and Osteoset, which are designed to be mixed with antibiotics chosen by surgeons [6]. Calcium sulfate beads may offer improved outcomes for patients requiring revisions of total hip and knee arthroplasty. They are biodegradable and can disappear on radiography within an average of 31 days [7]. In vitro and in vivo studies have shown locally eluted concentrations of vancomycin and tobramycin that are >10 times greater than minimal inhibitory concentration with nominal systemic toxicity [1, 2, 8].

The efficacy data for calcium beads alone are mixed. A retrospective case series of 250 THA/TKA analyzed patients treated with beads comprised of 1 g of vancomycin and 240 mg of liquid tobramycin per 10 cc of calcium sulfate powder (Stimulan) over 2 years. Outcomes showed an overall low failure rate of 9/250 (3.6%) with a 1.2% incidence of heterotopic bone formation and a 3.2% incidence of wound drainage. The failure rate was inclusive of all interventions, including aseptic revisions, 2-stage septic revisions with PMMA spacers, and 1-stage debridement modular exchange, component retention, and parenteral antibiotic (DECRA). However, they also reported 2 cases of acute renal failure (ARF), with 1 requiring 3 weeks of dialysis [7]. No specific postoperative antibiotic regimen or serum antibiotic levels was reported, and PMMA spacers were used in tandem with beads for both hip and knee resection arthroplasties [6]. Efficacy concerns have been raised with the use of calcium sulfate beads alone in a retrospective review of 32 patients over 2 years undergoing I&D with implant retention for acute hematogenous or acute postoperative hip or knee PJI [9]. Surgeons utilized a preparation consisting of 10 cc of calcium sulfate with 1 g of vancomycin and 1.2 g of tobramycin, per manufacturer recommendations, and parenteral antibiotics were given afterwards for a minimum of 6 weeks. At a mean follow-up at 13 months, a total of 16/33 (48%) had reoccurrence of infection. Seven patients required subsequent 2-stage exchange, whereas another 8 patients opted for chronic antibiotic suppression. The authors concluded that calcium beads offer no additional clinical benefit over I&D alone in terms of implant retention.

In addition, although the risk of AKI from antibiotic spacers is well known, the safety data on calcium sulfate beads and their impact on parenteral treatment are less well characterized. To our knowledge, this case has the highest reported serum tobramycin and vancomycin levels attributed to calcium sulfate beads and resultant acute tubular necrosis. Although serum levels are expected to be elevated in the first 24 hours, this tobramycin serum level was sustained for over a week and was well above the safe trough threshold (<2 mg/dL) [9]. Known adverse side effects of calcium beads include heterotropic bone formation, hypercalcemia, and wound drainage. One case study (n = 15) reported 3/15 (20%) cases of transient hypercalcemia and 1 case of heterotrophic bone formation. One of the hypercalcemia cases required washout and treatment with 4 mg of parenteral zoledronic acid. These cases utilized 10 cc of 1-g vancomycin and 240-mg gentamicin mixed with sterile water, followed by 6 weeks of parenteral antibiotics. No serum vancomycin or gentamicin was drawn [7]. Clinicians should expect a minor increase in parenteral vancomycin levels as well. In treatment

of primarily Osteoset vancomycin beads (2 g of lyophilized vancomycin in 25 g of calcium sulfate), serum levels showed a small spike of 3–5 mg/L at 24 to 72 hours postsurgery that persisted at 240 hours postsurgery. However, in 3 cases of AKI, all 3 levels were found to be in the therapeutic range of 10–20, implying that this level would be even higher in an AKI patient pretreated with vancomycin. The authors noted that 7 patients did use Osteoset T pellets with additional tobramycin but did not individually report outcomes on them [8]. The interplay of elevated systemic vancomycin levels on aminoglycoside toxicity is also unclear. It has been noted that vancomycin administration may worsen aminoglycoside toxicity by facilitating the adhesion of the brush border membrane of the proximal tubules to aminoglycosides or by addictive effects at similar places in the tubules [11–13].

We propose a standardized protocol to minimize nephrotoxicity, along with close calcium and serum creatinine monitoring postoperatively in patients with acute kidney injury. Risk factors based on those identified from studies on antibiotic spacer–induced AKI include the use of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, intraoperative administration of blood products and administration of piperacillin-tazobactam [13–15]. Postoperatively, nephrotoxic medications should be held for 24–72 hours barring clinical necessity. Our patient in particular only had a slightly elevated serum creatinine before surgery. We suggest that patients on parenteral vancomycin before surgery have corresponding levels rechecked in 24 hours and be closely followed thereafter. In conclusion, we emphasize that additional research needs to be done on the specific use of calcium sulfate beads alone for I&D and implant retention, as well as on the impact on recurrence of infection and long-term antibiotic resistance when used with spacers for 1- or 2-stage exchanges.

Acknowledgments

Financial support. There are no funding sources to be reported.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Howlin RP, Brayford MJ, Webb JS, et al. Antibiotic-loaded synthetic calcium sulfate beads for prevention of bacterial colonization and biofilm formation in periprosthetic infections. Antimicrob Agents Chemother **2015**; 59:111–20.
2. Dusane DH, Diamond SM, Knecht CS, et al. Effects of loading concentration, blood and synovial fluid on antibiotic release and anti-biofilm activity of bone cement beads. J Control Release **2017**; 248:24–32.
3. KDIGO AKI Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl **2012**; 17:1–138.
4. Kapadia BH, Berg RA, Daley JA, et al. Periprosthetic joint infection. Lancet **2016**; 387:386–94.
5. Osmon DR, Berbari EF, Berendt AR, et al; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis **2013**; 56:e1–e25.
6. McPherson EJ, Dipane MV, Sherif SM. Dissolvable antibiotic beads in treatment of periprosthetic joint infection and revision arthroplasty - the use of synthetic pure calcium sulfate (Stimulan®) impregnated with vancomycin & tobramycin. Reconstruct Rev **2013**; 3:32–43.
7. Kallala R, Haddad FS. Hypercalcaemia following the use of antibiotic-eluting absorbable calcium sulphate beads in revision arthroplasty for infection. Bone Joint J **2015**; 97-B:1237–41.
8. Wahl P, Guidi M, Benninger E, et al. The levels of vancomycin in the blood and the wound after the local treatment of bone and soft-tissue infection with antibiotic-loaded calcium sulphate as carrier material. Bone Joint J **2017**; 99-B:1537–44.
9. Flierl MA, Culp BM, Okroj KT, et al. Poor outcomes of irrigation and debridement in acute periprosthetic joint infection with antibiotic-impregnated calcium sulfate beads. J Arthroplasty **2017**; 32:2505–7.
10. Pham PA, Bartlett JG. Tobramycin. Johns Hopkins antibiotic guide. https://www.unboundmedicine.com/ucentral/view/Johns_Hopkins_ABX_Guide/540556/all/Tobramycin?q=tobramycin&ti=0#9.1. Accessed 29 December 2017.
11. Salim SA, Everitt J, Schwartz A, et al. Aminoglycoside impregnated cement spacer precipitating acute kidney injury requiring hemodialysis. Semin Dial **2018**; 31:88–93.
12. Wood CA, Kohlhepp SJ, Kohnen PW, et al. Vancomycin enhancement of experimental tobramycin nephrotoxicity. Antimicrob Agents Chemother **1986**; 30:20–4.
13. Menge TJ, Koethe JR, Jenkins CA, et al. Acute kidney injury after placement of an antibiotic-impregnated cement spacer during revision total knee arthroplasty. J Arthroplasty **2012**; 27:1221–7.e1.
14. Reed EE, Johnston J, Severing J, et al. Nephrotoxicity risk factors and intravenous vancomycin dosing in the immediate postoperative period following antibiotic-impregnated cement spacer placement. Ann Pharmacother **2014**; 48:962–9.
15. Aeng ES, Shalansky KF, Lau TT, et al. Acute kidney injury with tobramycin-impregnated bone cement spacers in prosthetic joint infections. Ann Pharmacother **2015**; 49:1207–13.