

Acute Onset of Vancomycin Anaphylaxis With Disseminated Intravascular Coagulation in an Orthopedic Patient Despite Prior Repeated Exposure

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Abstract

Vancomycin is a glycopeptide antibiotic that exhibits bactericidal activity against gram-positive cocci. It is commonly recommended for surgical prophylaxis in cases of suspected bacterial resistance or penicillin allergy. There are 2 main types of hypersensitivity reactions associated with vancomycin. Red man syndrome is an anaphylactoid reaction caused by direct release of histamine. The second is an anaphylactic reaction, which is an immunoglobulin E–mediated response.

We present the case of a 55-year-old woman with a history of metastatic giant cell tumor of the right proximal tibia. She had undergone multiple surgeries for this and other nonorthopedic conditions. The patient received vancomycin for the majority of these procedures and extended courses of vancomycin on 2 separate occasions. In the present case, the patient was taken to the operating room for a prosthetic infection, and vancomycin was given after cultures were taken. The patient immediately developed signs consistent with anaphylaxis and disseminated intravascular coagulation. This was treated acutely with hemodynamic resuscitation, replacement of blood components, steroids, and repeated boluses of epinephrine. She recovered and was taken back to the operating room during that same admission without incident. The patient has since been treated with systemic daptomycin and a tobramycin cement spacer without further incident.

Vancomycin is a glycopeptide antibiotic that exhibits bactericidal activity against gram-positive cocci. It is commonly recommended for surgical prophylaxis in cases of suspected bacterial resistance or penicillin allergy.¹ Two main types of hypersensitivity reactions associated with

vancomycin can have similar presentations. Red man syndrome is an anaphylactoid reaction caused by direct release of histamine from mast cells via a nonimmunologic mechanism, and is the more common of the 2 reactions. The second type is an anaphylactic reaction, which is an immunoglobulin E (IgE)–mediated systemic event and requires exposure to become sensitized.^{2,3}

We present a patient who had received vancomycin on at least 12 occasions without incident. On this occasion, however, she developed a true anaphylactic reaction causing acute hemodynamic collapse that she survived after extensive resuscitation. The patient provided written informed consent for print and electronic publication of this case report.

Case Report

A 55-year-old woman had a history of metastatic giant cell tumor of the right proximal tibia. She was originally treated 27 years ago for proximal tibial resection and reconstruction with a custom proximal tibial prosthesis. Four months later, she underwent resection of multiple pulmonary metastases via bilateral thoracotomies in a single surgical setting. After this, the patient had no evidence of recurrent metastatic disease. In subsequent years, the patient underwent multiple revision surgeries for problems such as hardware failure, patellar maltracking, and infection. The patient underwent 19 operations, including several nonorthopedic procedures. Because the patient had a rash after receiving penicillin as a child, she was thought to be allergic to penicillin. Consequently, she received vancomycin as antibiotic prophylaxis for the majority of these procedures. She also received extended courses of vancomycin of at least 6 weeks on 2 separate occasions. During her most recent revision procedure, 6 weeks prior to the procedure under discussion, the patient took vancomycin without incident. She was then found to have a prosthetic infection with *Staphylococcus epidermidis*, the same organism isolated in her previous infections, and she was advised to undergo a staged revision.

After a preoperative medical evaluation by her primary care physician, the patient was taken to the operating room

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for prosthesis removal and antibiotic spacer placement. She was anemic with a hemoglobin level of 8.8 g/dL; her erythrocyte sedimentation rate (ESR) was 102 mm/h (normal, <22 mm/h) and her C-reactive protein (CRP) was 38 mg/L (normal, <3 mg/L), but, otherwise, her laboratory values were normal, including a white blood cell count (WBC) of 8100/ μ L. Her electrocardiogram showed a normal sinus rhythm with nonspecific ST- and T-wave changes. Antibiotics were held until after cultures were taken. General endotracheal tube anesthesia was induced with 2 mg midazolam, 100 μ g fentanyl, 180 mg propofol, and 140 mg succinylcholine, followed by 10 mg vecuronium, and maintained with desflurane. A tourniquet was not used per the surgeon's routine. Dissection was carried down to the prosthesis and showed a small amount of purulent fluid. Transfusion of 1 unit of packed red blood cells (pRBC) was started during the approach owing to relatively low preoperative hemoglobin and significant blood loss. Approximately 500 mL of blood was lost during the approach secondary to the extensive dissection and the local inflammatory response from infection and recent surgery. After cultures were taken, and approximately 10 minutes after blood transfusion began, infusion of 1 g vancomycin in 250 mL normal saline was started via an infusion pump to run over 1 hour.

After infusion of 5 mL vancomycin, the patient's blood pressure dropped from 117/63 mm Hg to 63/30 mm Hg; her pulse concurrently dropped from 90 to 50 beats/min. Vancomycin infusion was immediately stopped, anesthesia gasses were turned off, and patient received a bolus of normal saline with a second unit of pRBC. Patient received boluses of 0.5 mg to 1.0 mg epinephrine and 100 μ g phenylephrine without sustained increase in blood pressure, which had dropped to 54/24 mm Hg, although the patient became tachycardic to ~120 beats/min after epinephrine. A sudden drop in end-tidal CO₂ from 40s mm Hg to 20s mm Hg was also noted, indicating continuous but significantly decreased perfusion of the lungs.

We elected to abort the procedure, and a vacuum-assisted closure (VAC) dressing was applied to the open wound. After 15 minutes, the patient's pulses, which had been faint, became impalpable, and cardiopulmonary resuscitation was initiated for about 7 minutes. The patient received 40 units vasopressin with repeated boluses of 0.5 mg epinephrine; a norepinephrine continuous infusion was started with the return of pulses. The patient also received 50 mg diphenhydramine, 125 mg methylprednisolone, and 20 mg famotidine for suspected anaphylaxis. A central venous line and arterial line were placed, and blood was drawn for laboratory analysis. The patient was noted to have clear breath sounds with no obvious rash, and her urine remained clear. Blood gas showed a profound metabolic acidosis, with pH of 7.09, base deficit of 5.9, and lactate of 8.9. The patient was treated with bicarbonate infusion. The patient was noted to ooze significantly during central venous line and arterial line placement, despite apparently normal coagulation during the surgical approach. Coagulation values were consistent with disseminated intravascular coagulation

(DIC): prothrombin time, 57 s (international normalized ratio, 6.7); partial thromboplastin time, >200 s; thrombin time, 110 s; D-dimer, >10,000 ng/mL (normal, 0-200 ng/mL); and fibrinogen, <60 mg/dL (normal, 222-475 mg/dL). The patient's thromboelastogram showed a flat line indicating an absence of clotting. Interestingly, the platelet count remained near the preoperative level at $338 \times 10^3/\mu$ L. The patient's blood pressure remained labile and was responsive primarily to epinephrine boluses, of which she received a total of 5 mg. After 1 hour of resuscitation, during which time the patient received a total of 5 L crystalloid and 3 units pRBC, the patient was transferred to the intensive care unit (ICU), intubated, and started on a titrated epinephrine infusion.

Upon arrival in the ICU, the patient quickly stabilized hemodynamically. She was weaned from all inotropic support within 2 hours of arrival. The patient lost 800 mL of blood through wound VAC over the first 12 hours postoperatively and required a total of 11 units of pRBC, 6 units fresh frozen plasma, and 3 units of pooled cryoprecipitate, all of which were compatible. Laboratory values, including arterial pH, lactic acid, and coagulation studies, normalized on the evening of surgery, and, by the next morning, the patient was alert and was extubated without difficulty. Steroids were tapered without hemodynamic compromise while the patient was in the ICU. Cardiology examination revealed no abnormalities. Because of the temporal association of blood transfusion with cardiovascular collapse, pRBC units were retested for antibodies and cultured. Both of these investigations were negative. Wound cultures again were positive for *Staphylococcus epidermidis*, and blood cultures were negative. The patient was started on daptomycin based on susceptibility profiles. Serum histamine levels taken during initial resuscitation in the operating room were normal. The serum tryptase level obtained at the same time was markedly elevated at >700 ng/mL (normal, <11.5 ng/mL), although this information was not available until several days later.

The patient underwent 2 additional surgeries during the same admission, including the prosthesis removal and tobramycin cement spacer placement, without incident. She was discharged home, again without incident. The patient was later evaluated by an outside allergist and underwent skin puncture and intradermal allergy testing. The results were consistent with a strong IgE-mediated hypersensitivity. Interestingly, she was found not to have a penicillin allergy.

Discussion

Vancomycin hypersensitivity reactions include the anaphylactoid reaction red man syndrome and a true IgE-mediated anaphylactic reaction. Red man syndrome is much more common, with reported rates in infected patients from 3.7% to 47%,^{4,5} when vancomycin is given at the suggested rate of 1 g over 1 hour. The reaction occurs because of histamine release from mast cells and basophils, and does not require previous sensitization.³ The rate of infusion is directly related to the development of symptoms, with 100% of patients developing symptoms in 1 study with rapid infusion

(1 g over 10 min).⁶ Red man syndrome can typically be prevented by slowing the rate of infusion or by giving an H₁ blocker.³ Anaphylaxis is more rare but can occur.⁷ Anaphylaxis is mediated by vancomycin-specific IgE, which requires previous exposure, as was the case with our patient. Interestingly, the patient had received vancomycin many times without any signs of a hypersensitivity reaction. Antihistamines are not effective in treating anaphylaxis, and epinephrine is the first-line agent.³ This was clearly demonstrated in this case, as there was a significant hemodynamic response to epinephrine and a negligible response to other vasopressors, specifically norepinephrine and vasopressin.

Most hypersensitivity reactions during the course of a surgical procedure occur with induction of anesthesia, with neuromuscular blocking agents and antibiotics being the most common causes.⁸ In our case, antibiotics were held until after deep cultures were taken. Given the time from induction to the anaphylactic reaction, it is unlikely the reaction resulted from the induction agents or the neuromuscular blocking agent. The possibility of a transfusion reaction was also investigated, since a unit of pRBC was still being transfused when symptoms began. An acute hemolytic transfusion reaction has the classic triad of fever, flank pain, and hemoglobinuria, and can also present as DIC.⁹ Under anesthesia, DIC can often be the presenting sign. In this case, a hemolytic transfusion reaction appeared very unlikely. All of the blood components the patient received were rechecked and found to be compatible, posttransfusion analysis showed no evidence of hemolysis in any sample, and the direct antiglobulin test was negative in all components.

To our knowledge, there are no reported cases of vancomycin-induced anaphylaxis with concomitant DIC. Symptoms of anaphylaxis after exposure to a possible antigen include rapid onset of hypotension or rapid onset of signs in at least 2 organ systems, including cutaneous, gastrointestinal, respiratory, and cardiovascular.¹⁰ Anaphylaxis with DIC is rare after exposure to any substance but has been reported.¹¹ In fact, induction of systemic anaphylaxis in mice is known to cause DIC, with platelet-activating factor suggested as an important common mediator. A similar mechanism is suspected in humans.¹²

Confirmation of, and, certainly, prediction of, a vancomycin hypersensitivity reaction is difficult. Histamine levels can be used as a measure of mast-cell degranulation, but serum levels peak within 5 minutes and quickly return to baseline, limiting its diagnostic usefulness.³ Tryptase is an enzyme found in the secretory granules of mast cells. It has become an accepted marker of acute anaphylaxis, and, in vancomycin hypersensitivity reactions, can also distinguish between anaphylactic and anaphylactoid reactions.¹³ Tryptase levels peak 1 to 2 hours after the reaction, making this easier to measure than histamine, but results may not be available for several days, making it useful only in retrospect, as in our case. Skin testing is probably the best way to confirm a hypersensitivity reaction, although even this has been questioned with vancomycin because some find a high false-positive rate³, while others think the false-negative rate is likely too high.⁷ In this case, we were able to confirm our

initial clinical suspicion with both an elevated tryptase level and a positive skin test.

Conclusion

We present a rare case of vancomycin anaphylaxis with DIC after repeated and prolonged previous exposure, which was treated acutely with hemodynamic resuscitation, replacement of blood components, steroids, and, most importantly, repeated boluses of epinephrine. Although several papers have described successful vancomycin desensitization⁷, this was fortunately not necessary in this case because the causative organism was sensitive to other acceptable antibiotics. The patient has been treated with systemic daptomycin and a tobramycin cement spacer without further incident.

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