
Vancomycin anaphylaxis and successful desensitization in a patient with end stage renal disease on hemodialysis by maintaining steady antibiotic levels

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Background: Vancomycin anaphylaxis is a major management problem in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis. Lerner et al in 1984 have described a protocol for desensitization to vancomycin; however, antibiotic blood levels have never been used as a guide in this process.

Case Report: A 46-year-old female with ESRD on hemodialysis who developed a dialysis-catheter related MRSA sepsis was found to have anaphylaxis to vancomycin. She underwent successful desensitization to vancomycin using Lerner's protocol. Periodic antibiotic blood levels were used to guide the amount and frequency of vancomycin infusion to successfully maintain desensitization thereafter.

Discussion: Lerner described loss of desensitization to vancomycin when antibiotic infusion was stopped after 18 hours followed by successful desensitization to the same drug via the same protocol. This observation points out that desensitization to vancomycin appears to be dependent on some minimal drug level. In our case report, we have for the first time used the concept of blood levels to maintain successful desensitization to an antibiotic.

Conclusion: We hypothesize that desensitization to vancomycin can be induced and maintained by keeping a minimum antibiotic blood level. Further studies are needed to quantify this.

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INTRODUCTION

Vancomycin is a narrow-spectrum glycopeptide antibiotic with potent anti-staphylococcal activity. It is excreted via the kidneys. In patients with end stage renal disease (ESRD) its excretion is delayed. Vancomycin can pro-

duce two different types of immediate reactions. The more common type is the 'Red Man Syndrome' which is a non-IgE-mediated reaction.² The second reaction, which is much less frequently seen, is IgE-induced anaphylaxis. Lerner et al have reported successful desensitization protocol for vancomycin. In their report, they describe loss of desensitization to vancomycin after the infusion was inadvertently discontinued for 18 hours on the 11th day of therapy followed by successful re-desensitization to the drug by the same procedure.³ We describe the first reported case of a patient with ESRD on hemodialysis who underwent vancomycin desensitization according to Lerner's protocol and subsequent maintenance by periodic infusions of vancomycin guided by drug levels.

CASE REPORT

MC was a 46-year-old morbidly obese female with ESRD secondary to IgA nephropathy. She was undergoing hemodialysis three times a week for the last year. She was admitted to the hospital with dialysis catheter-related methicillin resistant *Staphylococcus aureus* (MRSA) sepsis determined by multiple positive blood cultures. She had a history of reactions to multiple antibiotics including vancomycin. The type of reaction to vancomycin was thought to be 'red man syndrome' as she experienced flushing only. She was in the emergency department and was not undergoing hemodialysis on this admission. She was given vancomycin 1 g in 500 milliliters of normal saline (NS) at 100 mL/h after pretreatment with 25 mg of diphenhydramine hydrochloride. This is a frequently used technique of slow infusion for red man syndrome. Within 2 minutes of the start of this slow infusion, she developed severe difficulty breathing, extensive wheezing, cyanosis, hypoxemia (oxygen saturation dropped to 74% on room air), extensive pruritis, and erythema all over the body. She improved clinically on cessation of vancomycin infusion and treatment with 25 mg more of diphenhydramine hydrochloride. The described reaction was consistent with anaphylaxis.

The MRSA isolated from the blood cultures was sensitive to few antibiotics, including vancomycin and rifampin. She was transferred to the intensive care unit where she was desensitized to vancomycin according to Lerner protocol,³ which is as follows:

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The patient received methylprednisolone 60 mg every 6 hours, diphenhydramine hydrochloride 50 mg every 6 hours, and famotidine 20 mg every 12 hours. Following this, 10 mL of standard vancomycin solution (500 mg in 250 mL of NS) was serially diluted to prepare four 100 mL solutions with concentrations of 1:10, 1:100, 1:1000, 1:10000 of the original concentration. Normal saline was used as the diluent for all these solutions. The 1:10000 solution was first infused at a rate of 0.5 mL/min for 15 min and if tolerated the rate was doubled every 15 minutes until the goal of 5 mL/min was achieved. The above sequence was followed for each increment in concentration (1:1000, 1:100, and 1:10 in that order). She tolerated the desensitization well without any adverse effects. At this point intravenous methylprednisolone and diphenhydramine were discontinued. Famotidine was however continued for the purpose of peptic ulcer prophylaxis. Immediately after desensitization she received 1 g of vancomycin in 500 mL of NS as an infusion starting at 0.5 mL/min, doubling every 15 minutes to achieve a rate of 5 mL/min and continued until completed. She remained asymptomatic throughout these infusions. The vanco-

mycin level measured after 18 hrs of the above infusion was 7.9 μ g/mL.

Subsequently, random vancomycin levels were monitored periodically and antibiotic administered in attempt to keep levels therapeutic (Table 1).

The patient did not have any reactions to vancomycin throughout the treatment period following desensitization. She unfortunately deteriorated clinically, developing a large pneumonia as demonstrated by the chest roentgenogram on the 5th day of admission. She required intubation over the next few hours for worsening respiratory symptoms and impending respiratory failure. Sputum culture and urine culture grew MRSA. During her hospitalization she had a total of six blood cultures positive for MRSA. Transesophageal echocardiogram did not show any endocardial vegetations or abscesses. On the 9th day of admission *Enterobacter cloacae* grew in one of the sputum cultures and was treated with Imipenem. On the 13th day of admission the chest roentgenogram showed multiple round cavities which were not present on the computed tomography scan (CT Scan) of the chest two days prior. She underwent bronchoscopy, which revealed large amounts of purulent secretions bilater-

ally. On the 14th day she went into cardiac arrest and was pronounced dead after unsuccessful resuscitation. Autopsy proved that the cause of death was bilateral staphylococcal pneumonia and overwhelming sepsis.

DISCUSSION

Vancomycin is the drug of choice in the treatment of methicillin resistant staphylococcal infections. A unique adverse reaction called the 'red man syndrome' occurs with rapid infusion of large doses of the antibiotic. It is the most common adverse reaction to vancomycin.² It is thought to be due to vancomycin-induced release of histamine without the involvement of preformed antibodies. It is usually treated by diluting the vancomycin solution and administering it over a longer duration of time. In one previously reported case, this did not help but sequential increments in vancomycin administration over several days was attempted successfully.⁴ Allergic skin reactions may occur in up to 5% of patients on vancomycin.² Although the exact incidence is not known, anaphylactic reactions involving preformed IgE antibodies are rare with vancomycin but can occur.² There are few case

Table 1. Random Vancomycin Levels Taken Periodically During the Stay in the Hospital and Amount of Vancomycin Administered

No.	Date	Time	Random Vancomycin Level (μ g/mL)	Amount of Vancomycin Infused
1	6.15.98	8:26	7.9	350 mg in 250 mL NS over 2 hr after HD
2	6.16.98	3:48	13.6	1 g in 250 mL NS over 4 hr after HD
3	6.17.98	13:11	17.0	350 mg in 250 mL NS over 2 hr after HD
4	6.18.98	3:21	21.7	
5	6.19.98	4:10	15.0	500 mg in 250 mL NS over 4 hr after HD
6	6.20.98	4:24	20.2	500 mg in 250 mL NS over 4 hr after HD
7	6.21.98	12:43	21.8	500 mg in 250 mL NS over 4 hr after HD
8	6.22.98	5:01	24.5	
9	6.23.98	10:04	17.8	350 mg in 250 mL NS over 4 hr after HD
10	6.24.98	11:35	24.9	

List of acronyms and abbreviations used in the table: NS: normal saline and HD: hemodialysis. Abbreviation and acronym list: ESRD: end stage renal disease, MRSA: methicillin-resistant *Staphylococcus aureus*, NS: normal saline, and CT scan: computed tomography scan.

reports concerning vancomycin desensitization.^{3,5}

Vancomycin is excreted through the kidneys. Consequently its elimination in patients with ESRD is protracted. In one study the elimination half-life was approximately 7.5 days compared with 6 to 8 hours in normal individuals.¹ The nonrenal route of vancomycin clearance in anephric patients is uncertain and has not been studied extensively. Numerous studies have shown that high flux dialyzers do in fact clear vancomycin to a certain extent. Studies have not been done, but it has been known that even high efficiency dialyzers like the one that was used for daily hemodialysis on our patient can also clear vancomycin to a variable extent. This could explain the fact that she required almost everyday vancomycin infusion to keep her blood levels therapeutic. A nomogram for vancomycin dosage in patients with impaired renal function has been described by Moellering et al.⁶

At the time of her initial reaction the patient was pretreated with diphenhydramine before vancomycin infusion was given. Despite this she developed a fairly severe anaphylaxis to vancomycin. We strongly believe that epinephrine should have been given to the patient in view of the above finding. The emergency room physician however did not do this while the patient was under his care, a decision that we cannot account for due to lack of our involvement in patient care at that point of time.

Skin test to detect and document the presence of specific IgE antibody against vancomycin was considered but not employed because she was already pretreated with H₁ blockers that may have resulted in a false negative skin reaction. Hence a negative skin reaction would not have in any way precluded the need for desensitization. A positive skin test, however, would have been extremely useful. It would have clarified that the patient had IgE antibodies to vancomycin and that the initial reaction was unequivocally an anaphylactic reaction. Although never

proven, her anaphylaxis in the emergency department could have been to vancomycin only, as supported by the temporal relation between onset of the reaction and vancomycin infusion.

Since our case report is anecdotal, we did not originally intend to use antibiotic serum levels to maintain desensitization. Consequently, antibiotic blood levels were not drawn at finite times. Also, due to everyday use of 'high efficiency' dialyzers, which are known to clear vancomycin to a variable extent and a very large volume of distribution related to the patient's body mass, it was impossible to keep track of peak and trough vancomycin levels. Although we think that there is a minimum antibiotic blood level required to maintain desensitization, further studies need to be done to quantify this.

The patient's worsening respiratory status on the 5th day of hospital stay could have been less likely due to an allergic reaction but was more consistent with staphylococcal pneumonia and overwhelming sepsis. This is supported by the fact that she developed a large pneumonia, which later grew out MRSA at the time of her respiratory symptoms as confirmed by a chest roentgenogram. She grew MRSA in multiple blood cultures and urine culture consistent with sepsis. Furthermore, on autopsy it was proven that the cause of death was bilateral staphylococcal pneumonia and overwhelming sepsis. High doses of steroids could not have contributed to this deterioration because they were discontinued after desensitization procedure was completed.

In the original article describing the vancomycin desensitization protocol, Lerner et al described loss of desensitization to the drug when on the 11th day of vancomycin therapy the drug infusion was stopped inadvertently for 18 hours. Subsequently, the patient was again successfully desensitized to the drug via the same protocol. Assuming normal renal function, and taking into account the 6-hour half-life of vancomycin, the drug levels will be very low 18 hours after a full strength

dose of vancomycin is administered. This observation points to the hypothesis that desensitization to vancomycin is dependent on some minimal drug level in blood. Our case is the first reported in literature in which the idea of antibiotic blood levels was utilized to maintain successful desensitization to an antibiotic (Ovid and Medline searches). Hence by presenting this case we hypothesize that desensitization to vancomycin can be induced and maintained by keeping a minimum antibiotic level.

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