Successful Vancomycin Desensitization with a Combination of Rapid and Slow Infusion Methods

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Abstract

Vancomycin, an antibiotic to which methicillin-resistant *Staphylococcus aureus* (MRSA) is sensitive, frequently induces hypersensitivity reactions. Lowering the vancomycin infusion rate and/or premedicating with antihistamine effectively reduce hypersensitivity in most cases. However, vancomycin desensitization is sometimes the only way to ensure safe use. Two types of desensitization protocols have been reported, and these utilize different infusion intervals; rapid desensitization and slow desensitization. We herein report a case of vancomycin hypersensitivity with methicillin-resistant *Staphylococcus aureus* infection. A combination of the two desensitization protocols, rapid desensitization followed by slow desensitization, effectively inhibited the hypersensitivity reaction during vancomycin infusion, and methicillin-resistant *Staphylococcus aureus* was successfully eradicated.

Key words: vancomycin, desensitization, hypersensitivity

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) induces sepsis, endocarditis, pneumonia and soft tissue infection and is difficult to treat because of the limited range of antibiotics to which MRSA is sensitive. Vancomycin is one of the effective antibiotics against MRSA, but vancomycin is associated with many adverse effects, including hypersensitivity reactions. There are two types of hypersensitivity reaction to vancomycin; an anaphylactoid reaction known as “red man syndrome” (RMS) and anaphylaxis (1).

RMS involves non-immunological histamine release following rapid infusion of vancomycin and consists of pruritus, skin flushing in the upper chest, head and neck, and occasionally, hypotension. Lowering the vancomycin infusion rate relieves the symptoms and premedication with antihistamine is effective in preventing RMS. On the other hand, anaphylaxis is an immunologic reaction mediated by immunoglobulin E (IgE) and is independent of the infusion rate. Readministration of vancomycin during anaphylaxis may cause respiratory arrest and thus desensitization is the only way to safely use vancomycin.

Several authors have reported desensitization protocols for vancomycin hypersensitivity (2-8). The reported protocols vary in the initial infusion rate and the duration of infusion, and can be classified into two types depending on the infusion interval; rapid desensitization and slow desensitization. In rapid desensitization, the time and dose necessary for desensitization can be decreased, but increases in the infusion rate over short periods of time may trigger sudden hypersensitivity reactions.

Here, we report a case of vancomycin hypersensitivity with MRSA infection. Although hypersensitivity reactions were observed during rapid desensitization, switching to slow desensitization led to successful MRSA eradication.

Case report

A 43-year-old man was admitted to our hospital complaining of wound pain in his back on May 14, 1999. He had a history of intervertebral disk herniation beginning in 1995. In February 1998, discectomy and duraplasty were performed and a prosthetic spacer was inserted at the surgic-
Table 1. Vancomycin Desensitization Protocol. For Rapid Desensitization, 50 ml of Vancomycin Solution (500 mg in 50 ml Normal Saline) was Serially Diluted Tenfold to Produce Five 50-ml Solutions at Concentrations of 1:10, 1:100, 1:1,000, 1:10,000 and 1:100,000. Vancomycin was Slowly Administered, Starting with the Highest Dilution at a Rate of 1.0 ml/min (Vancomycin Infusion Rate 0.0001 mg/min) for 10 minutes. Next, a more Concentrated Solution was Administered at a Rate of 0.33 ml/min (Vancomycin Infusion Rate 0.00033 mg/min) for 10 minutes. Rapid Desensitization was Completed in 110 minutes. For Slow Desensitization, the Remainder of the 500 mg of Vancomycin was Administered at an Infusion Rate of 4.4 mg/min on Day 1. On Subsequent Days, 500 mg of Vancomycin in 500 ml of Normal Saline was Infused Over a Period of 300 minutes.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Concentration (mg/ml)</th>
<th>Infusion rate (mg/min)</th>
<th>Cumulative dose (mg)</th>
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<tr>
<td>1-10</td>
<td>0.0001</td>
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<td>10-20</td>
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<tr>
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<td>1.00</td>
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<td>110-215</td>
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<td>3.00</td>
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Physical examination on admission revealed the following: blood pressure, 120/80 mmHg; heart rate, 76 beats/min; temperature, 36.7°C. The wound on the back was exudative and about 10 cm in length. The right tonsil was painful and swollen with white plaques. There was no skin eruption and no abnormal respiratory sounds were noted. Laboratory data revealed a leukocyte count of 9.2 x 10^9/L with an eosinophil proportion of 1%, aspartate aminotransferase (AST) levels of 36 IU/L and alanine aminotransferase (ALT) levels of 59 IU/L on liver function test, and serum creatinine levels of 0.9 mg/dl and blood urea nitrogen levels of 12.4 mg/dl on renal function test. Wound culture and throat swab yielded MRSA that was sensitive to vancomycin. Spinal computed tomography revealed neither fluid nor high-density areas in the soft tissue around the L5-S1 disk. From these findings the patient was diagnosed as having pharyngitis and wound infection with MRSA.

On May 25, 1999, antibiotic therapy was initiated with 1 g of vancomycin for three hours twice a day. After the first 1-g infusion of vancomycin, flushing of the face and body was seen. Before the next vancomycin infusion, 6 mg d-chlorpheniramine maleate (H1 receptor antagonist) was administered, but his body temperature increased to 38.9°C and wheezing in the chest was heard during infusion. Administration of vancomycin was discontinued. Treatment with arbekacin and teicoplanin was then attempted. However, these treatments were not completed because liver dysfunction, eosinophilia and skin eruption were seen immediately after or within a few days of administration. At this point, MRSA was not eradicated and was still detected in the wound and throat.

Vancomycin desensitization was attempted using a rapid continuous desensitization protocol, as described by Wong (2). Before the start of vancomycin infusion, 6 mg d-chlorpheniramine maleate and 150 mg of ranitidine (H2 receptor antagonists) was administered orally. Vancomycin infusion was initiated at a rate of 0.0001 mg/min for 10 minutes. The infusion rate was increased 3- or 3.3-fold every ten minutes until the infusion rate reached 4.4 mg/min. Thereafter, vancomycin was administered at a rate of 4.4 mg/min and the total dose of vancomycin administered was 0.5 g (Table 1). Immediately after the first infusion, flushing of the face and body was seen and wheezing was heard in the chest, but this disappeared after several minutes. No symptoms were present before the infusion rate reached 4.4 mg/min. When vancomycin was administered at a rate of 4.4 mg/min, flushing of the whole body was similarly noted again. When administration of vancomycin was completed, his body temperature increased to 38.9°C and discharge and watering of the eyes were observed.

On the next day, these symptoms had improved, and thus vancomycin was administered at 0.5 g over five hours, according to the protocol of Lin (3). Flushing of the body and fever were again seen, but wheezing in the chest was not noted. Serum IgE was 78 IU/ml, which is within the normal range. Administration of vancomycin at 0.5 g continued at...
Figure 1. Clinical course of the patient. Cultures from the back wound and throat, degree of skin rash, and drugs and dosage administered for MRSA infection are shown in the upper panel. Changes in body temperature are shown in the lower panel.

Discussion

Hypersensitivity reactions to vancomycin include anaphylaxis and an anaphylactoid reaction known as RMS. According to the Gell and Cooms classification system, anaphylaxis is a type-I immune reaction that induces IgE-mediated release of histamine by mast cells and basophils (9, 10). The early phases of the anaphylactic reaction involve local edema, smooth muscle contraction, vasodilatation and increased permeability of postcapillary venules, while late reactions include urticaria, hypotension and bronchospasms (4, 5). Anaphylaxis is independent of vancomycin infusion rate, but occurs within 1.5 hours of vancomycin exposure. In contrast, RMS involves IgE-independent histamine release from mast cells or basophils (11). Clinical symptoms of RMS include generalized flushing, pruritus, erythematous rash, hypotension, dyspnea and chest pain (12). In addition, RMS is dependent on the vancomycin infusion rate (13). Tryptase, a component of mast cell granules, is elevated in the plasma of anaphylaxis patients, but not in the plasma of RMS patients (14, 15). However, it is sometimes difficult to distinguish between anaphylaxis and RMS.

In the present case, while changing the infusion rate of vancomycin, hypersensitivity reactions occurred twice. The first reaction occurred immediately after vancomycin administration and the second reaction occurred at the final infusion rate used in rapid desensitization. MRSA was eradicated from throat swabs and the back wound was almost completely healed on day 20 of desensitization. After treatment, recurrence of the symptoms on admission did not occur over a follow-up period of one year.

Vancomycin desensitization is indicated in anaphylaxis
and RMS (1). There have been seven vancomycin desensitization reports published, and these can be separated into two desensitization protocols based on the infusion interval: rapid desensitization and slow desensitization (2-8). Four different rapid desensitization protocols were used in five reports (2, 5-8), while the slow desensitization protocol was used by Lin (3), and was also applied to a patient who failed rapid desensitization in a report by Anne (4). In rapid desensitization, the interval between each step is 10 to 30 minutes and a period of 100 to 300 minutes is required to complete desensitization. In the slow desensitization protocol reported by Lin, vancomycin was administered at 0.001 mg/min for 5 hours on day 1 (3). Vancomycin was infused at a gradually elevating rate until the required dose of vancomycin was administered after 2 weeks.

Rapid desensitization is advantageous as both the time and dose of vancomycin required for completing desensitization are reduced compared with slow desensitization. Reducing the time required to achieve a normal infusion rate also results in more rapid achievement of therapeutic serum concentrations. If treatment is discontinued during desensitization because of anaphylaxis, small doses of vancomycin are easily cleared. However, in cases where anaphylaxis is delayed during rapid desensitization, rapid increases in serum vancomycin concentration may induce a severe hypersensitivity reaction. In RMS, which is dependent on the vancomycin infusion rate, a rapid increase in the infusion rate may suddenly trigger a hypersensitivity reaction. Many previous reports have not distinguished between anaphylaxis and RMS and because there are no reports of failed desensitization, the actual results for each protocol could not be estimated. Therefore, the ideal protocols for anaphylaxis and RMS may vary on a case-by-case basis. We initially adopted rapid desensitization, as reported by Wong et al, because the protocol required the shortest time to complete desensitization.

In most previous reports, allergic symptoms developed during desensitization (2-4, 6, 7). Wong reported that by transiently reducing the infusion rate hypersensitivity reactions were reduced (2). Anne reported that by switching to slow desensitization, treatment was successfully completed, as in the present case (4). Switching to slow desensitization facilitates maintaining vancomycin concentrations and allows time to observe and deal with changes in hypersensitivity reactions. However, starting with slow desensitization would require several days for serum concentrations to reach therapeutic levels and thus would increase the risk of emergence of vancomycin-resistant bacteria. Therefore, we believed that rapid desensitization should be indicated first, and that if hypersensitivity reactions occur during rapid desensitization, slow desensitization could be utilized.

Prophylactic administration of H1 receptor antagonists effectively decreases histamine release, and oral H1 receptor antagonists have been used in the prevention of RMS (18-21). However in acute anaphylaxis, antihistamines are not thought to be useful (1). In the present case, during the initial administration and prior to vancomycin desensitization, d-chlorpheniramine maleate was administered. With regard to H2 receptor antagonists, administration of cimetidine/ranitidine with H1 receptor antagonists does not appear to provide any significant benefit in ameliorating symptoms when compared with the use of H1 receptor antagonists alone (20). However, in preventing hypersensitivity reactions, pretreatment with a combination of H1 and H2 antagonists is more effective than with H1 antagonists alone (22). In the present case, H2 receptor antagonists were not preadministered for the first vancomycin administration, but ranitidine was used during vancomycin desensitization. We believed that pre-treatment with a combination of H1 and H2 antagonists may also be more effective for continuing vancomycin treatment. Epinephrine inhibits histamine release and antagonizes histamine-induced vasodilatation and capillary permeability. However, no studies have investigated the effects of epinephrine in preventing anaphylaxis due to vancomycin. Corticosteroids are not effective during acute anaphylaxis. In the present case, epinephrine and corticosteroids were not administered during the treatment.

In conclusion, we report a case of vancomycin hypersensitivity with MRSA infection. A combination of rapid desensitization and slow desensitization made it possible to continue administering vancomycin and finally led to MRSA eradication.

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References