CLINICAL CASE REPORTS

Severe vancomycin-induced anaphylactic reaction

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Summary. *Vancomycin is widely used against methicillin-resistant Staphylococcus aureus infections, but it is associated with many adverse effects such as nephrotoxicity, ototoxicity, gastrointestinal disturbances, blood disorders, and two types of hypersensitivity reactions – an anaphylactoid reaction known as "red man syndrome" and anaphylaxis. We report a case of a 23-year-old man who developed a vancomycin-induced anaphylactic reaction in the treatment of methicillin-resistant Staphylococcus aureus infection.*

Introduction

Vancomycin is a glycopeptide antibiotic exhibiting bactericidal activity against gram-positive cocci, as well as methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococci, *Clostridium difficile*, *Actinomyces*, *Bacillus anthracis*, *Corynebacterium*, *Listeria*. MRSA-induced sepsis, endocarditis, pneumonia, soft tissue infections are difficult to treat because of the limited range of antibiotics. Vancomycin is one of the most effective antibiotics against MRSA, but it is associated with many adverse effects. Adverse effects of vancomycin are nephrotoxicity including renal failure and interstitial nephritis, ototoxicity (vancomycin should be discontinued if tinnitus occurs), gastrointestinal, blood disorders including neutropenia (usually after 1 week or cumulative dose of 25 g); agranulocytosis, thrombocytopenia, and phlebitis have been reported rarely. Vancomycin-induced hypersensitivity occurs much more often: in 5–14% of treated children and 1.6–35% of adults (1). However, the number of such cases reported in literature is limited.

Two types of hypersensitivity reaction to vancomycin have been described: an anaphylactoid reaction known as "red man syndrome" (RMS) and anaphylaxis (2). We report a case of hypersensitivity to vancomycin therapy with MRSA infection, which we identified as anaphylaxis.

Case report

A 23-year-old man suddenly got ill, his body temperature rose up to 39˚C, soreness of the throat and muscle pain occurred. Examination revealed no abnormal findings in the internal organs; only abscesses in 5 roots of teeth were discovered. The diagnosis was unclear, and different therapy with penicillin, ceftriaxone, oxacillin, metronidazole, and meronem was unsuccessful. Suspecting the presence of Still's disease, treatment with oral prednisolone at a dose of 60 mg/day was started, and after 4 days, intravenous methylprednisolone pulse-therapy (at a dose of 1.0 g/day, 3.0 g in total) was added. Treatment with meronem and vancomycin was continued.

After 2 days of therapy, the patient developed renal and hepatic failure with a clinical picture of hepatic encephalopathy. Necrotic pharyngitis, hemorrhagic syndrome (a fine petechial rash in both the forearms and the chest area), and respiratory insufficiency occurred. The temperature rose again to 38.2˚C. Chest x-ray revealed still persisting signs of pleuritis as well as perivascular edema and pericarditis. Since drug toxicity affecting multiple organs could not be excluded, antibiotic therapy with meronem (1.0 g t.i.d., 27 g in total) and vancomycin (1.0 g b.i.d., 14 g in total) was discontinued, and steroids were continued orally as well as intravenously at a dose of 500 mg/day (for a total of 5 days). The condition started to improve: the patient's body temperature and respiratory function returned to normal, repeated chest x-ray showed decreasing signs of pleuritis and pericarditis. Renal function returned to normal within 3 days; hepatic function normalized within 12 days.

After 3 days, hectic fever reoccurred. A central venous catheter placed 23 days ago was removed.

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Blood and catheter-tip cultures were taken. Chest x-ray revealed development of focal medium-size infiltration in the middle of the left lung. Vesicular rash was observed on the skin. The condition was considered as fungal sepsis, and treatment with caspofungin was started. After 2 days, on completion of the bacteriological analysis of blood cultures, *Candida albicans* was detected. The culture of the catheter-tip was positive for *Enterococcus faecalis* and MRSA susceptible to vancomycin.

A decision to administer vancomycin was made. Vancomycin (1 g) was dissolved in 250 mL of isotonic solution. The infusion at a rate of 10 mg/min was started. Within the first minute of the drug administration, the patient developed a cold sweat, trembling occurred, face flushed, the tremor involving all the body, dyspnea, and tachycardia developed, blood pressure dropped to 80/60 mm Hg, skin rash was observed. The condition was considered as the anaphylactic reaction. The infusion was stopped. Clemastine, analgin, intravenous prednisolone at a dose of 60 mg, oxygen therapy, and crystalloid infusion (sol. Ringeri, sol. Isotonici) were administered. After 20 minutes, dyspnea and tachycardia disappeared, blood pressure and facial flushing got stable; however, the body tremor continued for 1 hour more, the patient's temperature rose to 39.5˚C. C-reactive protein (CRP) level was 69.09 mg/L. Repeated blood cultures showed no growth of bacteria. Ultrasound of the heart did not reveal any signs of endocarditis or pericardium fluid.

Linezolid (600 mg b.i.d. intravenously, for a total of 11 days) was administered for the further treatment of staphylococcal and enterococcal sepsis. Caspofungin was continued for the treatment of fungal sepsis (for a total of 12 days). Oral prednisolone was continued at a dose of 40 mg/day. The patient became apyretic, clinical and x-ray signs of lung injury, skin lesions disappeared, CRP returned to 28.64 mg/L (normal level). Results of the biopsy of the lymph node did not give sufficient data supporting presence of T-lymphoma or Kikuchi's syndrome. The diagnosis of the Still's disease was left unchanged. Prednisolone was gradually reduced to 20 mg/day and stopped after 4 weeks. The patient was discharged from the hospital with improved status.

Discussion

Hypersensitivity reactions to vancomycin include RMS and anaphylaxis. As far as it is known, the most common hypersensitivity reaction is RMS, with a reported incidence of 3.7% to 47% in infected patients and up to 90% in healthy volunteers (3–5). Anaphylactic reactions, on the other hand, are rare but do occur (2).

We performed a literature search in the PubMed and Cochrane library database using the key words *vancomycin anaphylaxis* and we found 41 articles on the mentioned topic. Only 8 articles represent true cases of vancomycin anaphylaxis. The results of our literature search of vancomycin-induced anaphylactic reactions are summarized in Table.

"Red man syndrome" (flushing limited to the neck and upper torso, pruritus, hypotension) is the best-known vancomycin-induced hypersensitivity reaction. This phenomenon occurs in case of too rapid injection of the drug and can be mistakenly attributed to allergy (1). The reaction usually disappears within 20 minutes, but sometimes persists for several hours.

RMS involves nonimmunological histamine release following a rapid infusion of vancomycin. It is related to histamine release-induced development of peripheral vasodilatation, which leads to hypotension, myocardial dysfunction, or direct inhibition of myocardial inotropic function. To prevent this syndrome, vancomycin should be injected slowly, at a rate not exceeding 10 mg/min, diluted with 50–100 mL of water for injections. Lowering the vancomycin infusion rate relieves the symptoms of RMS. Premedication with oral antihistamine has been used in the prevention of RMS (13–15). A combination of H_1 and H_2 antagonists is more effective than with H_1 antagonists alone (16).

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. However, in acute anaphylaxis, antihistamines are not thought to be useful (2). Thus, desensitization is the only way to safely use vancomycin.

In the present case, during the initial vancomycin administration, antihistamines were not administered; only clemastine (H_1 receptor antagonist) was added to the treatment when anaphylactic reaction occurred. Some investigators suggested that pretreatment with a combination of H_1 and H_2 antagonists might also be effective for continuing treatment with vancomycin (2).

Identification of a patient who is at risk of an immune reaction if given for a particular drug seems to be very important. To prevent the vancomycin-induced hypersensitivity syndrome, diagnostic methods

Table. Summary on published cases of vancomycin-induced anaphylactic reactions

Reference	Patient	Disease	Micro-organism	Concomitant disease	Symptoms	Outcome
Lognon et al., 1987 (6)	A 7-month-old male	Ventricular drainage catheter related sepsis	Methicillin-resistant *S. epidermidis*	n/a	Shock, bronchospasm, urticaria	Successful desensitization
Anné et al., 1994 (7)	A 47-year-old African-American female	Chronic osteomyelitis	MRSA	Acquired immunodeficiency syndrome	Generalized pruritus and severe burning sensation	Successful desensitization
Sorensen et al., 1998 (8)	A 47-year-old white female	Idiopathic hemorrhagic pancreatitis complicated by nosocomial pneumonia	Methicillin-resistant *S. epidermidis*	End-stage renal disease secondary to lupus erythematous nephritis on peritoneal dialysis	Laryngeal edema, neck thickening, tongue swelling, wheezing, respiratory discomfort, hypotension	Successful desensitization
Chopra et al., 2000 (9)	A 46-year-old female	Dialysis catheter-related MRSA sepsis	MRSA	Obesity, end-stage renal disease secondary to Ig A nephropathy, pneumonia	Respiratory discomfort, extensive wheezing, cyanosis, hypoxemia, extensive pruritus, erythema all over the body	Successful desensitization
Kitazawa et al.,	A 43-year-old male	Abscess	MRSA	n/a	Flushing of the face and body, wheezing	Successful desensitization
Wessel , 1998 (11)	A 47-year-old male	Orthopedic surgery, prophylactic use	–	n/a	Shock, bronchospasm	Successful desensitization
Villavicencio et al., 1998 (12)	A 43-year-old female	Draining-wound hematoma	MRSA	n/a	Acute shortness of breath, swelling of the face, lips, and eyelids, hypotensive shock, cardiovascular collapse	Successful desensitization

MRSA, methicillin-resistant *Staphylococcus aureus*.

such as skin prick test, intradermal skin test, basophile histamine release test have been used before administering the drug. However, skin tests show negative results in most of the cases (7, 17). The optimal concentration of vancomycin to be used in these tests has not been established yet. Based on data reported, 10% diluted vancomycin is used (18).

Unfortunately, the only reliable standardized predictive skin test at present is an intracutaneous or intradermal test for penicillin and insulin. Skin testing for other drugs is not standardized, in part because relevant antigens are not known and because many drugs induce nonspecific irritant reactions.

Radioallergosorbent test and enzyme-linked immunosorbent assay tests (looking for specific IgE in serum) are less sensitive than skin testing, and in almost all cases, the relevant drug antigens are not available for testing, generally because they are not known. In vitro or patch testing to detect other types of immune reactivity is neither predictive nor standardized (10).

Vancomycin is indicated for the treatment of serious, life-threatening infections by gram-positive bacteria, which are unresponsive to other less toxic antibiotics. In particular, vancomycin should be used in the treatment of serious infections caused by susceptible organisms resistant to penicillins (MRSA and multiresistant *Staphylococcus epidermidis* [MRSE]) or in individuals with serious allergy to penicillins and enterococci resistant to β-lactam-based antibiotics. Linezolid and teicoplanin are second-choice drugs in case if vancomycin-induced anaphylaxis is present. In our case, linezolid was proved to be an effective and safe drug for the mentioned treatment. The literature reports only one case of the patient with vertebral osteomyelitis and epidural abscess, who developed hypersensitivity syndrome to both vancomycin and teicoplanin (18).

Sunki vankomicino sukelta anafilaksinė reakcija

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Raktažodžiai: vankomicinas, anafilaksinė reakcija, nepageidaujama reakcija, pranešimas apie atvejį.

Santrauka. Vankomicinas yra plačiai vartojamas meticilinui atsparių stafilokokų sukeltoms infekcijoms gydyti. Jis yra nefrotoksiškas, ototoksiškas, taip pat sukelia nepageidaujamų reakcijų, tokių kaip virškinamojo trakto ir kraujotakos sutrikimai, dviejų tipų padidėjusio jautrumo reakcijas: anafilaktoidinę (žinomą kaip raudonojo žmogaus sindromą) ir anafilaksiją. Pateikiame klinikinį atvejį, kai gydant meticilinui atsparaus *Staphylococcus aureus* infekciją, 23 metų vyrui pasireiškė vankomicino sukelta anafilaksinė reakcija.

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