

Vancomycin induced Red man syndrome

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Abstract

Vancomycin is a glycoprotein antibiotic that has been associated with an anaphylactoid reaction termed the Red-man syndrome. It usually consists of erythema, flushing and pruritis of the face and upper torso and occasionally progresses to include dyspnoea, chest pain and hypotension. Vancomycin is an alternative drug for serious staphylococcal and streptococcal infections, including endocarditis, when allergy precludes the use of penicillins and cephalosporins. Vancomycin can cause two types of hypersensitivity reaction – the Red Man Syndrome (RMS) and anaphylaxis. Red man syndrome (RMS) is also known as “red neck syndrome. Discontinuation of the vancomycin infusion and administration of diphenhydramine can abort most of the reactions. Slow intravenous administration of vancomycin should minimize the risk of infusion-related adverse effects. Antibiotics such as ciprofloxacin, amphotericin B, rifampicin and teicoplanin can potentially cause red man syndrome. The effects of red man syndrome can be relieved by antihistamines.

Keywords: Antibiotic, Vancomycin, Red man syndrome, Anaphylaxis.

1. Introduction

1.1 Vancomycin

Vancomycin is an antibiotic discovered more than 50 years ago and used only for serious infections caused by gram positive organism. But last few years has witnessed the rapid resurgence of Vancomycin. The growing concern of rapidly spread of resistance in first line of antibiotic has dramatically sparked the uprising of Vancomycin. It acts by inhibiting cell wall synthesis and it was first found by Dr. E. C. Kornfield in 1952 in sample of mud send to him by a missionary in Borneo [1]. It is a glycopeptide antibiotic originally derived from *Streptomyces (Norcadia) orientalis*, is being widely used for severe Gram-positive bacterial infections, especially those caused by emerging strains of methicillin-resistant *Staphylococcus aureus* and coagulase-negative *staphylococci* [2].

Vancomycin is an alternative drug for serious staphylococcal and streptococcal infections, including endocarditis, when allergy precludes the use of penicillins and cephalosporins [3]. The most common vancomycin adverse effects are unrelated to serum drug concentration and include fever, chills, and phlebitis. A recent study conducted at six Korean pharmacovigilance centers (PVCs) reported that antibiotics including vancomycin were the most prevalent causes of ADRs, and that skin manifestations were the most common symptoms in spontaneously reported ADRs. Of the 1,418 cases in the study, 3.1% were associated with vancomycin [4].

Use of vancomycin may change the way blood cells are produced, and low levels of platelets might result, or white blood cell counts could change. In rare cases, the drug can damage the kidneys or damage hearing. These many potential risks, and there are many more, explain the limited use of this antibiotic. While it's good at eradicating certain infections, it can be hard on the body. It is important to note that many people tolerate this drug well, and are cured of very serious infections that resist treatment with other drugs [5].

Hospital Infection Control Practices Advisory Committee guidelines restrict use of vancomycin to the following indications

- Treatment of serious infections caused by susceptible organisms resistant to penicillins (Methicillin-resistant *Staphylococcus aureus* (MRSA) and multiresistant *Staphylococcus epidermidis* (MRSE)) or in individuals with serious allergy to penicillins
- Treatment of *pseudomembranous colitis* caused by *Clostridium difficile*; in particular, in cases of relapse or where the infection is unresponsive to metronidazole treatment (for this indication, vancomycin is given orally, rather than by its typical intravenous (IV) route)

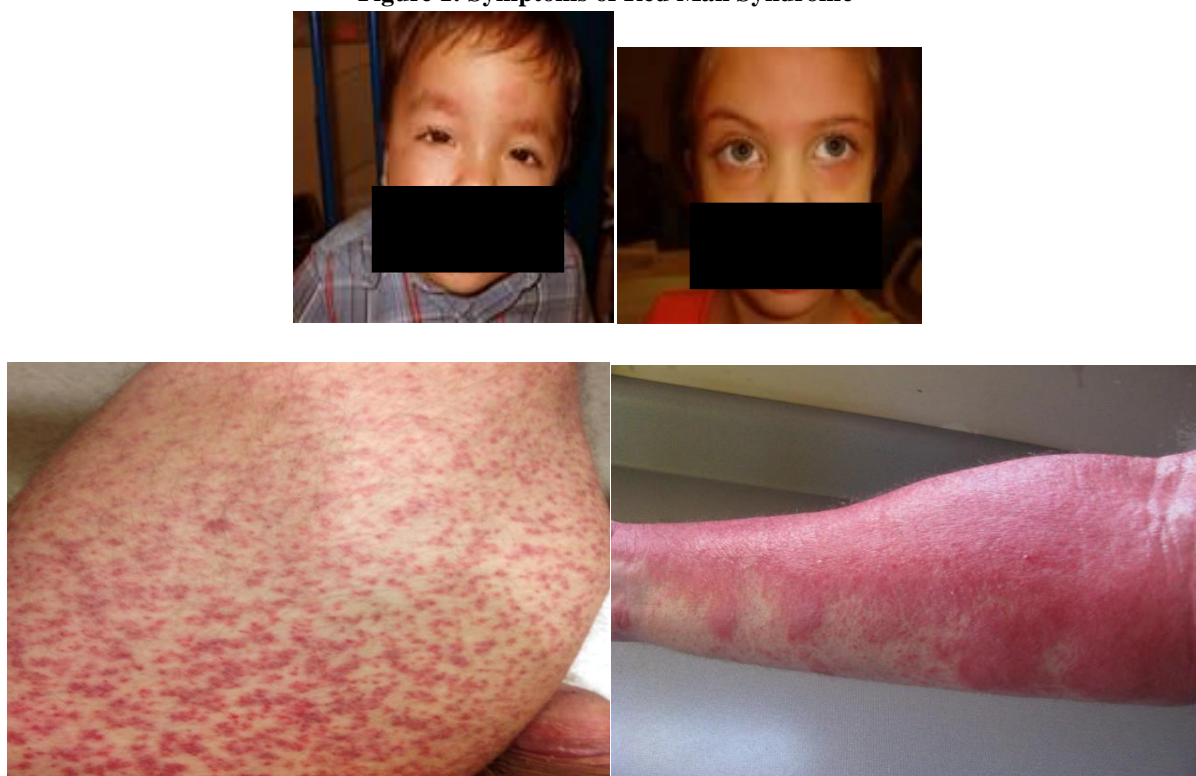
- For treatment of infections caused by gram-positive microorganisms in patients with serious allergies to beta-lactam antimicrobials.
- Antibacterial prophylaxis for endocarditis following certain procedures in penicillin-hypersensitive individuals at high risk
- Surgical prophylaxis for major procedures involving implantation of prostheses in institutions with a high rate of MRSA or MRSE
- Early in treatment as an empiric antibiotic for possible MRSA infection while waiting for culture identification of the infecting organism[6]

1.2 Red Man Syndrome

Vancomycin can cause two types of hypersensitivity reaction – the red man syndrome (RMS) and anaphylaxis. The most common vancomycin-related ADR is a cutaneous adverse reaction (i.e., RMS). RMS has been reported in 3.7-50% of infected patients and up to 90% of healthy volunteers [7]. Red Man Syndrome (RMS) is also known as “red neck syndrome” [8]. RMS is not thought to involve drug-specific antibodies and may develop even with the first administration of vancomycin. RMS is a form of pseudoallergic drug reaction, or an adverse drug reactions with signs and symptoms that mimic immunologic drug allergies, but in which immunologic mechanisms have not been demonstrated [9].

'Red man Syndrome' is thought to be an infusion-related reaction consisting of pruritus, an erythematous rash involving the face, neck and upper torso.

Figure 1: Symptoms of Red Man Syndrome



In milder form this reaction may be mistaken for an allergy, where patient commonly begins to experience itching and warmth over the head and chest, with or without the development of a rash and the condition may go unreported. Patients commonly complain of the sensations of burning and itching. Agitation, dizziness, headache, chills, fever and perioral paresthesia are also described. In severe cases patients complain of chest pain and dyspnoea[10]. Although the reaction is more likely to occur with rapid intravenous infusion of vancomycin, it may also occur when infusion is given at slower rate [11]. Signs of red man syndrome would appear about 4–10 min after an infusion started or may begin soon after its completion. The reaction may not be of the same severity with successive exposures, but it can occur for the first time after several doses or with a slow infusion [12].

Delayed reactions at or near the end of a 90 or 120 min infusion have been seen in patients who had been on vancomycin therapy for longer than 7 days without prior incident. Most of the hospital protocols require vancomycin to be infused over 60 min, as a minimum [13]. Sporadic reports of red man syndrome following the administration of vancomycin via routes other than intravenously are also on the increase. Red man syndrome has been linked to

intraperitoneal and oral administration of vancomycin. The most severe reactions occur in patients under 40 years old [14].

Red man syndrome is much more common, with reported rates in infected patients from 3.7% to 47%, when vancomycin is given at the suggested rate of 1 g over 1 hour [15]. Red man syndrome was in the past attributed to impurities found in vancomycin preparations, earning the drug the nickname 'Mississippi mud'[3]. Studies have shown that an unknown percentage of the population may be prone to releasing a large amount of histamine in response to vancomycin[16]. The hypersensitivity reactions that can arise due to vancomycin are due to its effect on the mast cells. In tissue culture, vancomycin causes degranulation of peritoneal mast cells in rats [17]. The anaphylactic reaction is mediated by IgE. Red man syndrome, an anaphylactoid reaction, is caused by the degranulation of mast cells and basophils, resulting in the release of histamine independent of preformed IgE or complement. The extent of histamine release is related partly to the amount and rate of the vancomycin infusion [18].

1.3 Connection between Vancomycin and Red Man Syndrome

Vancomycin kills a variety of bacterial pathogens. Red man syndrome is a hypersensitive allergic reaction that happens because the antibiotic interferes with immune system cells. In the case of vancomycin and Redman syndrome, the symptoms can be mild and are not life-threatening. Certain components of the immune system are responsible for causing these symptoms. Cells called mast cells and basophils contain storage granules of a substance named histamine. Histamine is one of the signal molecules of the immune system, and plays a role in the development of inflammation. Abnormally high levels of histamine in the circulation then causes the symptoms associated with Redman syndrome. The rash and itchiness represent an unnecessary activation of the immune system.

Only some people develop Redman syndrome, while others do not. Scientists think this is due to genetic differences between individual patients. For example, certain enzymes in the body naturally break down histamine. Two enzymes perform this role, which are histamine N-methyltransferase and diamine oxidase. Different people produce slightly different versions of these enzymes, that could have different efficiencies, and which may be one explanation for the absence of Redman syndrome in some people and the development of it in others. As well as potential genetic causes, other antibiotics can work in conjunction with vancomycin and increase the risk of Redman syndrome [5].

2. Causes

- The cause of Red Man Syndrome is a hypersensitive reaction occurring as a result of vancomycin infusion.
- Patient can develop this reaction, i.e., red man syndrome irrespective of the route of the vancomycin i.e. whether it is taken intraperitoneally (via an injection) or orally.
- Red Man Syndrome can also occur as a reaction to other medicines, such as antibiotics including rifampicin, teicoplanin, ciprofloxacin and amphotericin B. All these medicines which can cause Red Man Syndrome have a common element with vancomycin where they cause direct degranulation of the basophils and mast cells.
- Red man syndrome and its effects are more in cases where more than one medicine which can cause this type of reaction is taken.
- There are other drugs which can also trigger histamine release. So, red man syndrome is often worse in patients who not only have received vancomycin, but also muscle relaxants, contrast dye, or opioid analgesics.

3. Signs & Symptoms

The symptoms of the red man syndrome are very crucial to detect it. The reactions of the body should be immediately stopped once Red Man Syndrome has been identified by avoiding the drugs. However, the symptoms of the disease often go unnoticed and thus it is very important to observe.

The following are some of the symptoms of red man syndrome:

- Redness and rashes are the most common symptoms of the Red Man Syndrome. The rashes can be noticed in the back of neck, arms, upper portion of the body, back and even in the face. Itching on the rashes is very important as well for Red Man Syndrome.
- Nausea and vomiting are also crucial symptoms or parameters to identify the Red Man Syndrome. Hives are also associated with it. The patient suffering from Red Man Syndrome becomes very weak and starts showing lack of appetite.
- Low Blood Pressure often troubles the patient in case of Red Man Syndrome. It can also create fast heartbeats and uneasy feelings. It has been noticed that the Red Man Syndrome can even cause shortness in breath or breathlessness.
- Fainting/loss of consciousness.
- Feeling of Fever and Chills are also an indicator of the Red Man Syndrome as a reaction to the drugs.
- Weakness, muscle fatigue and dizziness are also very common symptoms of the disease. However, the Red Man Syndrome can even cause frequent faintness or unconsciousness.

○ Even though it is not very common but Red Man Syndrome can even cause Angioedema and Hypotension.

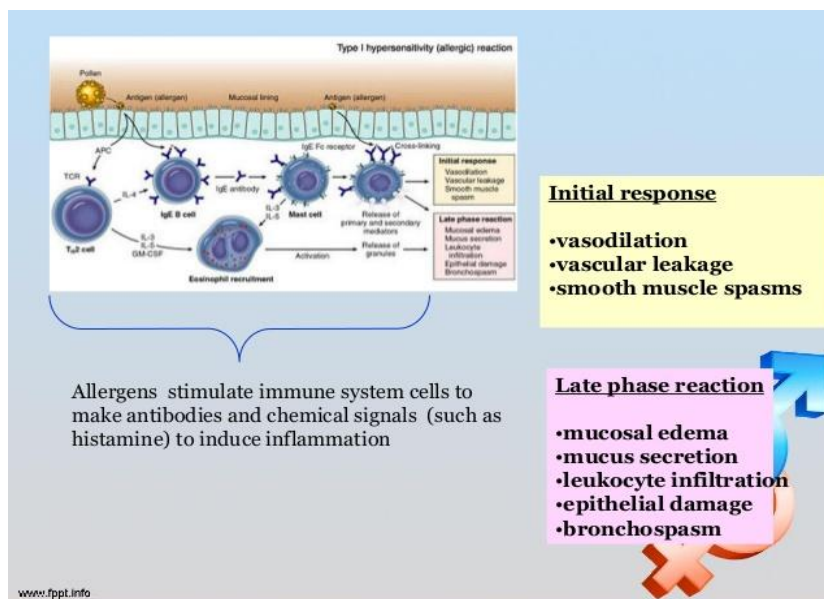
The symptoms are based on the health conditions of the patients and other factors. There have been situations where Red Man Syndrome has induced Dyspnoea, Muscle Spasm and even severe pain in the chest or in back. However, the symptoms are not so common and not frequently seen among the patients.

3.1 Occurrence of Symptoms in Red Man Syndrome

- Patients commonly start developing symptoms of Red Man Syndrome in about five to 10 minutes after their first vancomycin infusion starts. However, symptoms can also develop shortly after the infusion is complete.
- In majority of the cases, it is thought that red man syndrome develops because of the rapid infusion of the first dose of vancomycin, which is defined as less than an hour.
- The reaction or the severity of the Red Man Syndrome can vary each time the patient is exposed to vancomycin or other medicines. There are some patients who will not have this reaction until after the patient has received multiple doses or has had a slow infusion.
- In some individuals who have had vancomycin therapy for more than seven days without any previous reaction can start exhibiting symptoms. This is known as a delayed reaction [19].

4. Pathophysiology

Red man syndrome is considered an anaphylactoid type reaction. Vancomycin may lead to a direct release of histamine from the degranulation of cutaneous mast cells. Altered histamine metabolism may contribute to the pathogenesis of hypersensitivity reactions; including RMS. Histamine is synthesized from L-histidine and primarily metabolized by histamine N-methyltransferase (HNMT) and diamine oxidase (DAO). Both of these enzymes are polymorphically expressed. Several single nucleotide polymorphisms (SNPs) in the H₁ and H₄ histamine receptors also have been described. It is known that certain SNPs in the H₄ receptor, which is expressed on mast cells, are associated with atopic dermatitis and pruritus. It is possible that one or more of these SNPs may contribute to altered function of these receptors [20]. The extent of histamine release is related to the amount of medication and rate at which vancomycin is infused. Higher doses and faster infusion times are more likely to result in red man syndrome [6].



5. Treatment

There are several options available for treating and/or preventing red man syndrome. If a patient develops red man syndrome, the infusion should be stopped immediately. The effects of red man syndrome can be relieved by antihistamines such as diphenhydramine 50 mg intravenously or orally. After the symptoms resolve, vancomycin can be used again. To prevent red man syndrome from reoccurring, the infusion rate should be slowed. Vancomycin should be administered intravenously over an infusion rate of at least 60 minutes [21]. More specifically, for every 500 mg of intravenous vancomycin, 30 minutes should be added to the infusion time [22].

In addition, pretreatment with antihistamines, specifically histamine H₁ receptor antagonists can prevent this syndrome. For example, hydroxyzine or diphenhydramine can be administered prior to the start of the vancomycin infusion which can significantly reduce erythema and pruritus. In addition, a combination of an H₁ receptor antagonist as well as an

H₂ receptor antagonist can offer protection against this infusion-related reaction with vancomycin. Other studies have shown that combining an H₁ receptor blocker with an H₂ receptor blocker such as cimetidine may help to prevent or reduce the risk of red man syndrome [13]. Finally, red man syndrome is not considered an allergic reaction because it is reasonable to expose a patient who has experienced red man syndrome to vancomycin once again. Therapy with a β -blocker before surgery has been found to be protective against hypotension caused by vancomycin infusion [23].

5.1 Management of acute RMS

The optimal management of RMS has not been determined in controlled trials. The approach outlined herein is based on the authors' clinical experience.

- For mild to moderate reactions (eg, the patient is uncomfortable due to flushing or pruritus, but hemodynamically stable and not experiencing chest pain or muscle spasm), we typically interrupt the infusion, treat with diphenhydramine (50 mg orally or intravenously), and ranitidine (50 mg intravenously). Symptoms usually subside promptly. The infusion can then be restarted at one-half the original rate.
- For severe reactions (eg, involving muscle spasm, chest pain, or hypotension) we stop the infusion, treat with diphenhydramine (50 mg intravenously) as well as ranitidine (50 mg intravenously), and IV fluids if hypotension is present. Once symptoms have resolved, the infusion can be restarted, and given over four or more hours. For future doses in such patients, we suggest repeat premedication with antihistamines before each dose and infusion over four hours.

Following RMS of any severity, the patient's medication list should be reviewed to determine if other predisposing medications (eg, opiates) can be identified and discontinued, before restarting the infusion [9].

6. Conclusion

Each intravenous dose of vancomycin should be administered over at least a 60 min interval to minimize the infusion-related adverse effects. Longer infusion times should be used in patients receiving doses considerably larger than 1 g vancomycin. Studies have shown that vancomycin is much better tolerated when it is given in smaller and more frequent doses [24]. In clinical situations where prolonged infusion times are often impractical, as in the intensive care unit or an operative setting, especially ambulatory orthopedic or emergency procedures, pretreatment with antihistamines combined with an H₂ receptor blocker can offer protection against this infusion-related reaction with vancomycin[13].

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