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Effectiveness and comprehensive study of vancomycin antibiotic on human heath: Current issue and perspectives

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ABSTRACT

Redman syndrome (RMS) is the most common allergic reaction to vancomycin. This syndrome mainly occurs because of either a rapid infusion of vancomycin or the first administration of the drug, also known as vancomycin flushing syndrome (VFS), The term Redman refers to the visual manifestation of the syndrome. RMS was named because of its characteristics symptoms, is the appearance of a red rash or redness on the skin. Affecting individual develop a red discoloration on their face, neck and upper body. It may also involve the lower extremities like the legs to a lesser degree. VFS would appear about 4-10 minutes after starting infusion and it may assist for 36-48 hour. The patient having vancomycin dose may be showing an occurrence of breathing related problems, for example a decrease in partial pressure of oxygen results in breathlessness and a sudden drop of vitals such as pulse rate and heart rate. Redman syndrome is an anaphylactoid, trigger by the mass cells and the basophile activation. This reaction does not involve the immune system antibody- IgE mediator response. The release of histamine and inflammatory mediator contributes to the presenting symptoms. The incidence and prevalence of Redman syndrome estimates shows that it occurs in approximately 3-47% of patients receiving vancomycin. This rate highlights the importance of promptly recognizing and managing the syndrome to minimize its impact on patient health and well-being.

1. Introduction

Red man syndrome (RMS) is the most common allergic reaction to vancomycin. It generally occurs during rapid infusion of vancomycin; only few cases have been reported as results of local vancomycin administration. We hereby report a rare case where RMS developed after insertion of vancomycin-loaded bone cement in a primary total knee replacement (TKR). Vancomycin is a bactericidal antibiotic with activity against most gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* [1]. Although RMS is known to be a rapidly infusion-related reaction, it may also occur when infused in a slow rate [2, 3]. Vancomycin can cause two types of hypersensitivity reactions, the red man syndrome and anaphylaxis [4].

The mechanism of action of vancomycin involves inhibiting bacterial cell wall synthesis through binding to the D-alanyl-D-alanine terminus of peptidoglycan precursors. This action disrupts bacterial cell wall formation, leading to cell lysis and eventual death of the microorganism. However, this mechanism also triggers an adverse reaction in susceptible individuals. The exact pathway by which vancomycin induces red man syndrome has yet to be fully understood. Some claim the rapid infusion of vancomycin triggers histamine release of basophils and mast cells in the skin and other tissues. This release of histamine results in vasodilation, leading to the characteristic erythematous rash seen.

"Red man syndrome" was proposed "for the sake of accuracy both in terms of sexual and anatomic distribution. Hypersensitivity reactions to vancomycin include RMS and anaphylaxis [6]. RMS is an anaphylactoid reaction caused by degranulation of mast cells and basophils after rapid infusion of vancomycin, resulting in the release of histamine [7]. It is characterized by flushing, erythema, and pruritis on face, neck, and trunk. However, more advanced responses, including fever, agitation, angioedema, tachycardia, hypotension, and even cardiovascular collapse, may occur in severe cases [8]. If red man syndrome appears then the vancomycin infusion should be discontinued immediately. A dose of 50 mg diphenhydramine hydrochloride intravenously or orally can abort most of the reactions. Once the rash and itching dissipate, the infusion can be resumed at a slower rate and/or at a lesser dosage.

Anaphylaxis is an immunologically mediated reaction involving drug-specific immunoglobulin E (IgE) antibodies and is independent of the infusion rate. Anaphylaxis in response to vancomycin administration is believed to be rare, although reactions involving angioedema, respiratory distress, and bronchospasm with evident drug-specific IgE [9].

In cases of anaphylaxis, antihistamines are not thought to be useful [10]. Anaphylaxis can be severe, generalized allergic, or hypersensitivity reaction that is life-threatening; administration of epinephrine should be considered as rapidly as possible once anaphylaxis is recognized [11]. In addition to vancomycin, antibiotics such as ciprofloxacin, amphotericin B, rifampicin, and teicoplanin can potentially cause RMS [12]. More importantly, RMS can be aggravated in patients receiving opioid analgesics, muscle relaxants, or contrast dye because these drugs may induce histamine release from mast cells [13]. Fortunately, most RMS can be treated or prevented by slowing the medication infusion and administering a histamine-blocking agent [14]. There are still uncertainties regarding the rate and mechanism of vancomycin delivery from bone cement. Several factors including the type of cement used, the amount of vancomycin loaded, and the method of preparation may influence the delivery of vancomycin [15]. The use of vancomycin-loaded bone cement is considered to be safe in both animal and clinical studies [16].The peak vancomycin concentrations in blood were achieved 6 to 24 h after implantation and were extremely low. In contrast, the concentrations of vancomycin in bone remain high throughout the first 6 months, which is an important characteristic for both curative and prophylactic treatment.

Figure 1: Vancomycin drug and their reaction on human body**.**

Figure 2: Symptoms of Red Man syndrome.

2. Symptoms of RMS

Patients commonly complain of diffuse burning and itching, and generalized discomfort. They can rapidly become dizzy and agitated and develop headaches, chills, fever, and Paresthesia around the mouth. In severe cases, patients complain of chest pain and Dyspnea. In many patients, the syndrome is a mild, short-lived pruritus that goes unreported at the end of the infusion.

Red man syndrome manifests through various cutaneous and systemic symptoms.

2.1 Cutaneous symptoms

These symptoms are a prominent feature of red man syndrome, characterized by various skin manifestations. RMS's two main cutaneous symptoms are erythema and flushing. Some individuals may experience pruritus (itching) and a burning sensation on the affected skin.

Erythema refers to the red discoloration of the skin. It occurs due to the vasodilatory effects of histamine released during the adverse drug reaction. Histamine is a potent inflammatory mediator that acts on blood vessels, causing them to widen. This dilation increases blood flow to the skin, resulting in redness. The severity of erythema can vary from mild to intense, covering a localized or widespread area of the body. Flushing is closely related to erythema and refers to sudden and temporary skin redness. A feeling of warmth usually accompanies it. It occurs due to the dilation of blood vessels caused by histamine release. The blood vessel widening allows more blood to flow near the skin's surface, producing visible reddening. Flushing can affect the face, neck, chest, and other body areas and may last several minutes to hour. Pruritus, or itching, is another common symptom experienced by individuals with red man syndrome. Histamine is a key player in the itch sensation. When histamine is released and binds to specific receptors on the skin's sensory nerve fibres, it triggers itching.

Along with pruritus, patients undergoing vancomycin therapy may feel a burning sensation on the affected area. The inflammatory response triggered by histamine can irritate the skin's nerve endings leading to the perception of burning sensation (Figure 2).

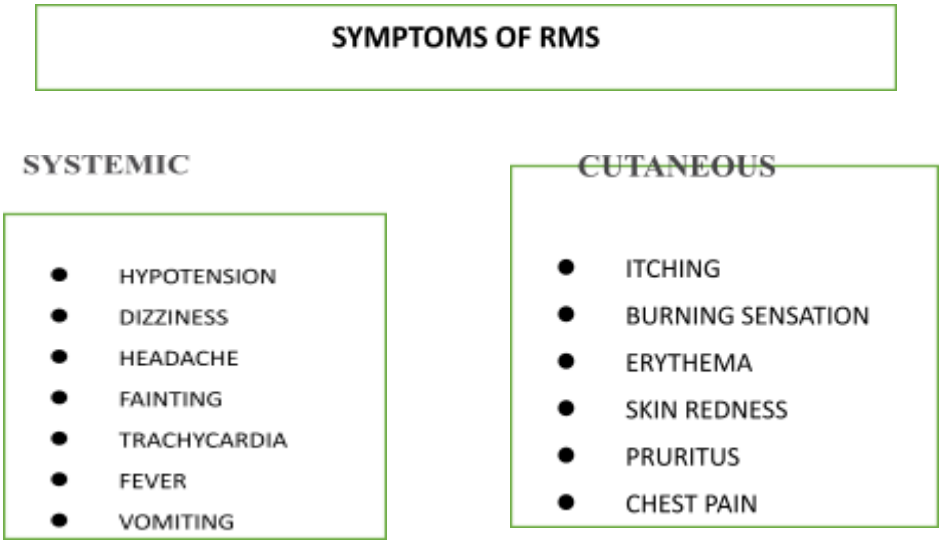

Figure 3: Cutaneous and systemic symptoms of (Red Man Syndrom) RMS

2.2 Systemic symptoms:

In addition to cutaneous symptoms, adverse effects of vancomycin can also manifest with various systemic symptoms. These symptoms can indicate a more severe reaction and require immediate attention for accurate diagnosis and prompt intervention.

Hypotension, or low blood pressure, is a notable systemic symptom of RMS. Histamine release during the adverse drug reaction can cause vasodilation, leading to a drop in blood pressure. Hypotension can result in symptoms such as dizziness, light headedness, and fainting. Severe hypotension can be dangerous and require urgent medical intervention to stabilize blood pressure.

Tachycardia, an abnormally fast heart rate, is another common systemic symptom. The release of histamine can affect cardiac function and lead to an increase in heart rate. Tachycardia can manifest as a rapid or pounding heartbeat accompanied by palpitations or unease. Monitoring heart rate is vital in assessing the severity of the reaction and guiding appropriate management.

Fever and chills can also be present in individuals with RMS. The release of inflammatory mediators, including histamine, can trigger an immune response that manifests as increased body temperature. Nausea and vomiting may occur as part of the systemic symptoms of RMS. The release of histamine can affect the gastrointestinal system, leading to feelings of nausea. In some cases, actual vomiting. These symptoms can contribute to dehydration and electrolyte imbalances.

3. Diagnosis for Red man Syndrome (RMS)

Diagnosing vancomycin-induced reaction involves clinical assessment, medical history review, and exclusion of other possible causes. The following steps are typically involved in the diagnosis and differential diagnosis of red man syndrome:

3.1 Patient evaluation: The healthcare provider begins by thoroughly evaluating the patient's symptoms and medical history. They inquire about the timing and duration of the symptoms, the medications administered, and any previous episodes of similar reactions.

3.2 Clinical presentation: Red man syndrome is primarily characterized by erythema and flushing of the upper body, particularly the face, and neck. The symptoms may be accompanied by itching, sensation of warmth, and occasionally, hypotension. It is important to note that the symptoms are usually limited to the upper body and do not involve respiratory or cardiovascular compromise, distinguishing it from true anaphylaxis.

3.3 Timing and drug administration: RMS typically occurs during or shortly after the infusion of vancomycin or other implicated medications. The timing of the symptoms in relation to drug administration can help establish a potential link.

3.4 Exclusion of other causes: It is crucial to rule out other possible causes of similar skin reactions or allergic responses. These may include true anaphylaxis, allergic or non-allergic drug reactions, and other drug-induced skin eruptions. Anaphylaxis, for example, involves a systemic allergic response that can lead to respiratory distress, hypotension, and other life-threatening symptoms. Differentiating red man syndrome from anaphylaxis is essential for appropriate management.

Skin biopsy (optional): Depending on the severity or case, a skin biopsy may be necessary to confirm the diagnosis and exclude other conditions. The biopsy may reveal nonspecific findings such as dilated blood vessels, mild inflammation, and edema.

4.Treatment of Redman Syndrome (RMS)

The immediate and essential step in managing red man syndrome is discontinuing administering the offending drug, most commonly vancomycin. This action helps prevent further progression of symptoms and minimize the risk of complications. The intravenous antibiotic infusion should be stopped immediately when a patient develops red man syndrome. Supportive care should be provided. Health professionals manage VFS with H1 (diphenhydramine) and H2 antihistamines (cimetidine). In most cases, future doses of vancomycin may be given at decreased infusion rates.

Mild cases (with less severe flushing and pruritus) can be managed with antihistamines such as diphenhydramine 50 mg by mouth or intravenously and cimetidine 300 mg intravenously. Most episodes will resolve within 20 minutes, and the vancomycin may be restarted at 50% of the original rate. Future doses should be given at the new, slower rate, typically over two hours.

Moderate to severe cases (severe rash, hypotension, tachycardia, chest pain, back pain, muscle spasms, weakness, angioedema) should be managed according to severity. Patients with severe symptoms should be evaluated for anaphylaxis or another serious cause for their symptoms before assuming vancomycin flushing syndrome (VFS). If, after careful evaluation, the patient is determined to have VFS, antihistamines such as diphenhydramine and cimetidine can both be started intravenously. Pharmacological interventions are often employed to provide symptomatic relief in cases of red man syndrome. These interventions include:

Antihistamines: Diphenhydramine can alleviate symptoms like flushing, itching, and rash. These medications block the effects of histamine released during the hypersensitivity reaction.

Corticosteroids: In some cases, corticosteroids may be given to reduce inflammation and suppress the patient's immune response associated with red man syndrome. They can help alleviate symptoms and promote faster resolution of the reaction.

Supportive care: In severe cases, supportive care such as fluids for hypotension and monitoring of vital science may be necessary. Intra venous fluids in more severe cases you might need IV fluids.

Alternative antibiotics: If Redman syndrome is severe or recurrent, alternative antibiotics should be considered if appropriate for the infection being treated.

5. Management of Red Man Syndrome (RMS)

5.1 For mild to moderate RMS: The patient is restless due to pruritus, but there is no complaints of chest pain or muscle spasm and even the patient is hemodynamically stable. Interrupt the infusion first and treat the patient with diphenhydramine (50 mg orally or intravenously) and ranitidine (50 mg intravenously) if the patient started to shown any kinds of manifestations. Usually the symptoms get subsided promptly after starting the treatment. After controlling the symptoms the infusion can then be restarted at one half the original rate.

5.2 For severe reactions: The patient complaints mostly about chest pain, hypotension and muscle spasm. Whenever you observe a severe reaction in patient followed by the intravenous infusion, stop the infusion immediately and treat the patient with both 50mg diphenhydramine and 50mg ranitidine intravenously. Provision of IV fluids is required if the patient is having low blood pressure. Once symptoms have resolved, the infusion can be restarted, and given over four or more hours.

5.3 Desensitization: Is treatment of choice for these type of patients. Desensitization is most commonly used in allergic reactions to various antibiotics that are due to true IgE- mediated mechanisms. Desensitization induces clinical "tolerance" to an agent when IgE-mediated mechanisms are responsible; the mechanism by which desensitization might work in non-IgE mediated reactions is not known.

5.4 Treatment of hypotension: Administration of a β- blocker is protective against hypotension caused by vancomycin infusion. Provide normal saline IV bolus and stop the infusion if the patient shows any signs of hypotension during the infusion.

6. Precaution

Use wet dressings, wet wraps or emollients to keep the affected skin always moist and healthy. It helps to protect the skin as well as to get relief from the manifestations. Use alternative antibiotics immediately if any other drug is available to replace vancomycin. If vancomycin must be continued, patients should be premedicated with diphenhydramine 50 mg intravenously and ranitidine 50 mg intravenously 1 hour before each dose, and vancomycin should be administered over 4 hours under close observation.

7. Differential Diagnosis

Both Red man syndrome and anaphylactic reaction has similar findings such as pruritis, erythematous rash, and tachycardia. Anaphylactic reactions show stridor, angioedema, hives and wheezing from bronchospasm. Anaphylactic reactions are IgE mediated and it requires prior exposure. However, RMS is a rate related anaphylactoid adverse reaction which most often occurs during the first exposure to IV vancomycin [17].

8. Uses of vancomycin antibiotics

Vancomycin can be used for the following reasons: Treatment of severe allergic reactions caused by gram-positive bacteria. It can also be used for treating endocarditis by using antibiotic prophylaxis.

Vancomycin can also be used to treat pseudomembranous colitis in cases where metronidazole therapy is not very effective. It can also be given as an intravitreal injection for treating endophthalmitis to give gram-positive bacterial coverage for the disease. It can also be used in major surgical prophylaxis procedures, such as prosthesis implantation. Vancomycin can also be given to a person resistant to penicillin and multi-drug therapy or severely allergic to penicillin antibiotics.

9. Side Effects of Vancomycin

Vancomycin is extensively used to treat various bacterial infections, but it can also produce some serious adverse effects, such as: Ototoxicity (hearing loss) with high or excessive doses and underlying causes like hearing loss or taking any ototoxic agent. Nephrotoxicity (kidney damage) usually causes renal impairment and renal failure and increases the creatinine level in the kidneys during therapy. Neutropenia (low white blood cells) occurs during the treatment with Vancomycin and subsides as soon as the treatment is completed.Eosinophilia (high eosinophil count). Phlebitis or vasculitis (blood vessel inflammation).

Case study

A 19 year old boy has complained of fever from the past next 2 weeks. He went for check up in the nearby hospital, doctor had advised him for typhoid test and he tested positive for typhoid IgM. The doctor has advice to took broad spectrum antibiotics MONOCEF 1g IV and PENTOP 40mg IV with probiotics in injectable form for a week. Then after a week the patient had the same complaints of fever, the temperature raised to 103-104 degree Celsius. There were no past history of smoking, alcohol, hypertension and drug allergy. ECG, Renal, Liver function tests were within normal limits. Since the patient was not known for diabetic and keeping in view of hospital acquired infection such as MRSA [Methicillin-resistant staphylococcus aureus], he was prescribed vancomycin 1g intravenous infusion with IV fluid and vitamin over twice a day. As soon as first dose of vancomycin was started, patient complained of Dyspnea , anxiety, chest pain, headache and was about to collapse. On examination, pulse was feeble, pulse rate 50 per minute and fall in blood pressure(70/40 mm hg) and heart beat drops to PO2=60. Immediately vancomycin infusion was stop and MONOCEF 1g IV with painkiller given intravenously with IV fluids. Patients recovered thereafter.

In the mid night 1 hour after the infusion of vancomycin the patients was on examination had same complaints, dyspnea, chest pain, headache. The vitals includes pulse rate was feeble, it was around 50 per minute, SPo2 is around 60, blood pressure also falls down(60/40 mm hg). Then the patients was put on the ventilator in the SICU[surgical intensive care unit] for 48 hours and there in the antibiotic infusion was stopped and diphenhydramine 50 mg was given intravenously with IV fluid. Patient’s vitals was checked every after few minutes. After 1 hour the patient was recovered.

Conclusion Vancomycin can cause two types of hypersensitivity reactions, the red man syndrome and anaphylaxis. Red man syndrome has often been associated with rapid infusion of the first dose of the drug and was initially attributed to impurities found in vancomycin preparations. Red man syndrome was in the past attributed to impurities found in vancomycin preparations, earning the drug the nickname 'Mississippi mud'. But reports of the syndrome persisted even after improvements in the compound's purity [18]. Studies have shown that an unknown percentage of the population may be prone to releasing a large amount of histamine in response to vancomycin [19]. 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 [20]. The extent of histamine release is related partly to the amount and rate of the vancomycin infusion. Clinical studies have shown that the plasma tryptase levels were not significantly elevated in confirmed anaphylactoid reactions, so they can be used to distinguish chemical reactions from immunologic reactions [21]. The most common hypersensitivity reaction associated with vancomycin is red man syndrome. The incidence varies between 3.7 and 47% in infected patients [22]. Studies of vancomycin also show that the most severe reactions occur in patients younger than the age of 40, particularly in children [23]. Other research has found that between 30 and 90% of healthy volunteers receiving vancomycin developed red man syndrome, while only about 47% of those with infections had the reaction [24]. One explanation for these results is that an infection induces some histamine release as part of the natural immune response. Having a higher histamine level to begin with is thought to downregulate vancomycin's effect on Mast cells and Basophils . Antibiotics such as ciprofloxacin, Amphotericin B, Rifampicin and teicoplanin [25] can potentially cause red man syndrome. Like vancomycin, they are capable of causing direct degranulation of mast cells and basophils. Red man syndrome is amplified if these antibiotics are combined with vancomycin or with each other [26]. Red man syndrome is also magnified in patients receiving vancomycin and opioid analgesics, muscle relaxants, or contrast dye because these drugs can also stimulate histamine release. The effects of red man syndrome can be relieved by antihistamines. Pre-treatment with hydroxyzine can significantly reduce erythema and pruritus [27]. Administration of diphenhydramine to patients before starting vancomycin infusion (1g over 1hour) can prevent the occurrence of red man syndrome with the first dose of vancomycin [28]. 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 [29].

In summary, 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 1g vancomycin. Studies have shown that vancomycin is much better tolerated when it is given in smaller and more frequent doses [30].In clinical situations where prolonged infusion times are often impractical, as in the intensive care unit or an operative setting, especially ambulatory orthopaedic or emergency procedures, pre-treatment with antihistamines combined with an H2 receptor blocker can offer protection against this infusion-related reaction with vancomycin.

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