



ISSN: 0975-833X

Available online at <http://www.journalcra.com>

INTERNATIONAL JOURNAL
OF CURRENT RESEARCH

International Journal of Current Research
Vol. 10, Issue, 12, pp.76485-76487, December, 2018

DOI: <https://doi.org/10.24941/ijcr.33472.12.2018>

REVIEW ARTICLE

RED MAN SYNDROME

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ARTICLE INFO

Article History:

Received 17th September, 2018
Received in revised form
21st October, 2018
Accepted 08th November, 2018
Published online 31st December, 2018

Key Words:

Red man Syndrome, Vancomycin,
Adverse Reaction, Glycopeptide
Antibiotic.

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Citation: Vinil Upendrababu. 2018. "Red man syndrome", *International Journal of Current Research*, 10, (12), 76485-76487.

ABSTRACT

"Red man syndrome" (RMS) or Red neck syndrome is the most common adverse reaction to vancomycin, characterized by flushing of the upper body, pruritus, mild to profound hypotension, chest pain, and muscle spasm. Rapid intravenous (IV) infusion of vancomycin, a glycopeptide antibiotic, is the most common cause of this syndrome. Even though it is not an allergic reaction, this syndrome most often looks like an Allergy. Some oral drugs, also, release histamine in the body which can result in red man syndrome nevertheless it occurs predominantly during parenteral administration of vancomycin. Discontinuation of the vancomycin infusion and administration of diphenhydramine can be useful to abort most of the symptoms. Slow intravenous administration of vancomycin should minimize the risk of infusion-related adverse effects. Hence Practitioners using vancomycin should be aware of this known drug reaction, its prevention, and treatment.

INTRODUCTION

Red Man Syndrome is a form of pseudo allergic 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 (Angela, 2012). In past RMS was attributed to impurities found in vancomycin preparations, earning the drug the nickname "Mississippi Mud". Red man syndrome is mainly occur either because of both rapid infusion of vancomycin or with the first administration of vancomycin (Khurana, 1999). Although the reaction is more likely to occur with rapid intravenous infusion of vancomycin, the incidence of RMS is also reported even with the slow infusion of vancomycin. This infusion-related reaction commonly present with pruritus, an erythematous rash involving the face, neck and upper torso. The common manifestations vary according to the severity of the problem. Usually the signs and symptoms of RMS begin either about four to ten minutes after an infusion started or may begin soon after finishing the full dose of drug administration. The reaction may not be the same severity with successive exposures. 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 minutes, as a minimum.

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As per the research findings, the occurrence of red man syndrome after the administration of vancomycin via routes other than intravenously are also on the rise. Red man syndrome is more common in infected patients when vancomycin given at the suggested rate of 1gm over 60 minutes (Vinay, 2011).

Incidence: As per the study reports the incidence of red man syndrome among infected patients is 3.7% to 47% and up to 90% in healthy persons. When infusion is given over less than one hour the incidence of RMS varies from 5 to 13% among patients on vancomycin. Most severe reactions are reported in patients with younger age in particular among children (Drisyamol, 2016).

Causes: The exact cause of red man syndrome is unknown in around 30% of patients.

Infusion of vancomycin: Rapid Intravenous infusion of vancomycin (1 gram in less than 1 hour) is the main cause of red man syndrome although it is reported rarely in slow administration of the same drug. Not only intravenous infusion but oral and intra peritoneal routes are also the risk factors of red man syndrome (George Panos, 2012). Current treatment recommendations are to administer vancomycin at a rate no faster than 1 gram/hour or 10 mg/min.

Other Predisposing medications: Red Man Syndrome can also occur as a reaction to other medicines, such as antibiotics including rifampicin, teicoplanin, cefepime, ciprofloxacin and

amphotericin B. All these medicines leads to the occurrence of red man syndrome when it causes direct degranulation of the basophils and mast cells. Mast cells may be more easily activated by vancomycin when combine with some other medications. The combination of vancomycin and opioids (eg, morphine, meperidine, codeine) enhances dose or rate-related mast cell degranulation. Adverse reactions can occur following administration of vancomycin in individuals with prior opiate administration, or conversely, in those receiving opioids with prior vancomycin administration. Similar interactions could theoretically occur between vancomycin and radiocontrast dye, some smooth muscle relaxants used in general anesthesia, and any other agents that potentiate mast cell degranulation (Juyal, 2015).

Another medical condition: Red man syndrome is also reported in people who already have some medical conditions such as lung cancer, HIV and in graft versus host disease.

Age: Red man syndrome is more common among children. More severe cases of Red man syndrome are reported in people under the age of 40 years and it is particularly very severe if it's occur among children.

Pathophysiology: The exact cause of Red man syndrome is unknown. 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 causes the symptoms associated with Redman syndrome. Studies has proved that Vancomycin leads to a direct release of histamine from the degranulation of cutaneous mast cells. This leads to altered histamine metabolism, which may contribute to the pathogenesis of hypersensitivity reactions; including RMS. Histamine is synthesized from L-histidine and primarily metabolized by histamine N-methyltransferase and diamine oxidase. 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 leads to altered function of these receptors (Kristian Thestrup-Pedersen, 1988).

The extent of histamine release is directly proportional 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 although there is incidence of RMS with the slow infusion also. Moreover, Studies in animals also indicate that vancomycin directly activates mast cells, resulting in release of vasoactive mediators, such as histamine. Studies result suggest that either that other mediators may be involved or that plasma histamine is not sufficiently sensitive marker for mast cell activation localized to the skin. However Red man syndrome is not a common condition as it doesn't occurs among a rare group of people. Researchers think this is due to genetic differences between individual patients. For example, certain enzymes in the Human body naturally break down histamine. Histamine N-methyltransferase and diamine oxidase are the two examples for such kinds of enzymes. Different people produce slightly different amount 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 (Maurice Levy, 1990).

Signs and symptoms: The symptoms of Red man syndrome often go unnoticed and mostly during the initial period, it resembles with allergic reaction. The reactions of the body should be immediately stopped once red man syndrome has been detected. Thus it is very important to inspect the manifestations of RMS at it's very beginning stage. Usually Red man syndrome begins 4 to 10 minutes from the start of the first dose of IV vancomycin. Nevertheless this case is also has been reported after finishing the dose of Vancomycin (delayed onset). RMS may occur from later doses as far out as 7 days. The reaction or the severity of the Red Man Syndrome can vary each time when the patient is exposed to vancomycin or other medicines. There are some patients won't have any reaction until the patient has received multiple doses or has had a slow infusion (Mark, 1991). The following are the some of the common manifestations of red man syndrome: Redness and rashes are the most common manifestations of the Red Man Syndrome. Rashes can be noticed obviously in the back of neck, arms, upper portion of the body, back and even in the face. Itching over the rashes also is common in patients. The patient suffering from Red Man Syndrome is usually very weak and most oftenly has the complaints of lack of appetite. Also, Nausea and vomiting are the crucial parameters to identify this problem among patients. Other clinical manifestations include Hives, Low Blood Pressure, fast heartbeats, uneasy feelings, shortness in breath or breathlessness, Fainting/loss of consciousness, Feeling of Fever and Chills, Weakness, muscle fatigue, muscle spasm, severe pain in the chest or in back and dizziness are also very common symptoms of the disease. Moreover, the Red Man Syndrome can even cause frequent faintness or unconsciousness. Even though it is not very common, Red Man Syndrome can even cause Angioedema at times among some patients. In some patients, who have had a vancomycin therapy for more than seven days, symptoms may exhibit very lately without any previous reactions. This is known as delayed reaction (Ron, 1988). The skin can appear flushed and become itchy and burning. The face, eyes, and lips can also swell. After a few days of developing red man syndrome, the skin can also thicken and begin to peel, either in large sheets or small flakes. This is more prominent on the palms and soles of the feet. If the syndrome occurs on the scalp, it can result in hair loss while in some patient's nails can become ridged and fall off. RMS is rarely life-threatening, though severe cardiovascular toxicity and even cardiac arrest have been reported. Rarely it's leads to swollen lymphnodes, dehydration and secondary infections. Nephrotoxicity and ototoxicity are also some of the common manifestation of Red man syndrome.

Management: Usually there is no need of any premedication in most of the patients who are receiving vancomycin for the first time at standard rates of infusion (≤ 10 mg/min) or ≤ 500 mg to 1 gram/ hour. Nevertheless, the health care providers are to be very cautious when they are providing vancomycin for the patients who are also receiving opioids or other medications that predispose to mast cell activation. Studies has suggested that the pretreatment with antihistamine is effective in reducing the incidence of severe form of RMS. Hence in case of emergency or in presurgical settings, if more rapid

infusions are required, it is mandatory to take premedication with antihistamines (diphenhydramine, 50 mg orally and oral cimetidine, ≤ 4 mg per kg) (Soupramanien, 2003).

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 show 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.

For severe reactions: The patient complains 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. 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. Rarely, some individuals experience recurrent and persistent symptoms, despite premedication and slow infusion rates. Mast cell / basophils easily get activated in these patients, this is the reason why these clients have recurrent incidence of RMS. 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. For reducing erythema and pruritus among patients it is advisable to administer antihistamines, specifically histamine H1 receptor antagonists (hydroxyzine or diphenhydramine) prior to the start of the vancomycin infusion. Moreover a combination of H1 receptor antagonist as well H2 receptor antagonist can offer protection against this infusion-related reaction with vancomycin.

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.

Other measures: Stop unnecessary medication if the patient is showing any signs and symptoms of RMS. Application of topical steroids are helpful in protecting the victim skin from cutaneous manifestations. 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.

Add corticosteroids and epinephrine to the treatment regimen when the patients is showing any signs of anaphylaxis: Hives, stridor, wheezing. Moreover avoid other predisposing medication with vancomycin when the patient started to show signs and symptoms of RMS (Wallace, 1991).

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 oftenly occurs during the first exposure to IV vancomycin (Yasunori Nagahama, 2018).

Prognosis: The prognosis for patients with RMS is excellent if the patient get proper management at correct time. Vancomycin may be used again after an episode of RMS. Administration of prophylactic drugs are useful to prevent the occurrence/ reoccurrence of manifestations among patients.

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