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Role of Clinical Pharmacist in Handling Vancomycin for the Prevention and Treatment of Red Man Syndrome

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ABSTRACT

The anaphylactoid reaction known as red man syndrome occurs during the degranulation of mast cells and basophils, which release histamine without the aid of complement or preformed IgE. The dosage and rate of the vancomycin infusion were to blame. Red man syndrome (RMS), also known as vancomycin flushing syndrome (VFS), is an infusion related response caused by vancomycin. VFS symptoms and indicators includes erythematous rash across the upper body, neck and face, vomiting, nausea, pruritis, hypotension, chills, fever, weakness, vertigo, muscle spasm in the trunk, back or chest pain, tachycardia, angioedema. Although a rash on the extremities is possible, it usually doesn't have the same severity as the rash on the upper body, neck and face. Clinical judgement was used to make the diagnosis, no laboratory or other testing was required. Therefore, the use of vancomycin as well as its treatment and prevention, should be known to healthcare practitioners. The diagnosis, differentiating treatments, and clinical pharmacist role in red man syndrome are discussed in this activity.

INTRODUCTION

Red man syndrome is an anaphylactoid reaction that results from the degranulation of mast cells and basophils, which releases histamine without the aid of complement or preformed IgE. The dosage and rate of the vancomycin infusion also influence the amount of histamine is released. Red man syndrome is a reaction to infusions that is caused by vancomycin [1]. Vancomycin is a tricyclic glycopeptide antibiotic that was first produced from the germ Streptococcus orientalis. Methicillin-resistant Staphylococcus aureus (MRSA) and other gram-positive bacterial infections are both treated and prevented using vancomycin. Additionally, it works well against infections caused by streptococci, enterococci, and methicillin-susceptible Staphylococcus aureus (MSSA) [2]. Numerous off-label and FDA-approved clinical uses exist for vancomycin [3]. Nowadays antibiotics are misused by dispensing it in over the counter without proper indications resulting in drug resistance and occurrence of unwanted adverse effects [4].

FDA-approved Clinical Uses

- *Clostridioides difficile*-associated diarrhea (oral administration) [5]
- *Staphylococcus enterocolitis*
- Pseudomembranous colitis
- Endocarditis: *Diphtheroid, Enterococcal, Staphylococcal,* and *Streptococcal* species
- Staphylococcal infections: septicemia, skin and soft tissue infections, bone infections, lower respiratory tract infections, etc.

Off-Label Clinical Uses

- Catheter-related infections [6]
- Community-acquired bacterial pneumonia
- *Clostridioides difficile* infection
- Neonatal prophylaxis for Group B streptococcus
- Intra-abdominal infections due to MRSA or ampicillin-resistant enterococci
- Bacterial meningitis

- Bacterial endophthalmitis (systemic or intravitreal administration)
- Native vertebral osteomyelitis
- Peritonitis
- Prosthetic joint infection
- Necrotizing skin and soft tissue infections
- Surgical prophylaxis
- Surgical-site infections

Pharmacology:

Vancomycin acts by inhibiting the polymerization of peptidoglycans in bacterial cell walls, resulting in a bactericidal effect [7].

Pharmacodynamics/Kinetics:

Route of administration: Intravenous, oral, rectal administration (off-label)

Inhibition of bacterial growth: Slowly bactericidal

PK/PD parameter: AUC: MIC

Absorption: Oral vancomycin has a bioavailability of less than 10%.

Onset of action: Vancomycin has a rapid onset of action with a serum peak concentration immediately following the completion of the intravenous infusion. The onset of action of oral vancomycin is currently unknown.

Distribution: Large volume of distribution (0.4 L/kg to 1.0 L/kg) in body tissues and fluids, excluding cerebrospinal fluid (CSF) with non-inflamed meninges

Protein Binding: approximately 55%

Metabolism: No evident metabolism (excreted unchanged)

Clearance: 0.71 mL/minute/kg to 1.31 mL/minute/kg in adults with normal renal function

Half-life: Vancomycin has a bi-phasic elimination half-life, with its initial half-life being relatively quick and a terminal half-life of 4 to 6 hours in healthy adults with normal renal function. The elimination half-life is significantly prolonged in patients with renal dysfunction. Close monitoring is necessary for these patients.

Excretion: Intravenous vancomycin injection is primarily eliminated by glomerular filtration in the kidney (75% via urine). Oral vancomycin predominantly gets excreted in feces.

Adverse drug reaction: Nephrotoxicity, hypotension, and hypersensitivity responses are three of the main side effects of intravenous vancomycin injection [8]. Vancomycin can cause a specific kind of hypersensitivity reactions known as Red man syndrome, also known as Vancomycin flushing syndrome (VFS), and anaphylaxis are two different types of hypersensitivity events that can be caused by vancomycin [9].

Vancomycin flushing syndrome (VFS) is an anaphylactoid reaction caused by the rapid infusion of the glycopeptide antibiotic vancomycin and the release of histamine from mast cells and basophils. A red rash, hypotension, tachycardia, angioedema, etc. are among the symptoms. VFS is typically found after faster infusion rates and after several days of transfusion, however, it can also be observed with slower infusion rates. The face, neck, and upper body are frequently covered in an erythematous rash with pruritus. Angioedema and hypotension can occur less frequently. Patients frequently express generalized discomfort as well as diffuse burning and itching. They may experience a sharp increase in agitation and dizziness, as well as headache, chills, fever, and paresthesia in the mouth. Patients with severe conditions report chest discomfort and dyspnea. The condition in many patients is a minor, transient pruritus that occurs at the end of the infusion but is unreported. Even while the majority of the cases are controllable, some can be fatal [10]. Practitioners using vancomycin should be knowledgeable of this reaction, its management, and prevention.

Epidemiology

The most frequent side effect of intravenous vancomycin is VFS. 4% to 50% of infected patients receiving intravenous vancomycin encounter it. The risk of severe VFS responses is greatest in patients under the age of 40. Along with a rash on the face, neck, and upper body, severe responses might cause angioedema, hypotension, tachycardia, weakness, muscular spasms, chest pain, and back pain. Typically, VFS is manageable and mild. VFS reactions that pose a hazard to life do occur occasionally [1].

Etiology

Vancomycin most usually causes VFS when administered intravenously, while it can also do so when administered orally or intraperitoneally [11]. It frequently occurs when vancomycin is infused quickly (1 gram in less than 1 hour). Vancomycin should be administered at a rate of no more than 1 gram per hour, or 10 mg per minute, as per the current therapy guidelines. VFS frequently begins 4 to 10 minutes after the initial intravenous dosage of vancomycin. It could start right after a dose is finished or later in the infusion. VFS may occur from doses administered later, even up to seven days later.

Vancomycin use has grown as a result of an increase in the prevalence of methicillin/oxacillin-resistant Staphylococcus aureus, multiresistant Staphylococcus epidermidis, penicillin-resistant Streptococcus pneumoniae, and metronidazole-resistant Clostridium difficile. Vancomycin is frequently prescribed to treat bacterial endocarditis, abscesses with cellulitis, infections of surgically implanted devices, postoperative wounds, and bacterial bloodstream infections related to central lines [12]. Other antibiotics like rifampin, cefepime, teicoplanin, ciprofloxacin, and amphotericin B have also been associated in case studies with VFS [13].

Pathophysiology

In 1952, vancomycin was found in soil taken from Borneo's jungles. The antibiotic's initial formulations were dark and lacked purification. As a result, vancomycin was sometimes referred to as "Mississippi mud." Clinicians initially believed that vancomycin impurities were the cause of VFS, otic toxicity, and renal toxicity. However, VFS was still noted even after vancomycin was purified. Vancomycin promotes the degranulation of mast cells and basophils, boosting histamine release, according to multiple human and animal studies. The rate and dose of vancomycin infusion have been linked to how much histamine is released. The metabolism of histamine may also be delayed as a result of the inhibition of the enzymes histamine N-methyltransferase and diamine oxidase, according to some studies that do not always link increased histamine levels with severe cases of VFS [14].

Symptoms and signs

VFS can manifest clinically in a variety of ways, from insignificant itching to occasionally life-threatening symptoms. Beginning four minutes after the start of the first dose and lasting up to seven days after the last dose, symptoms can appear. Patients who get intravenous

vancomycin for infections are at risk of developing VFS. VFS symptoms and signs include:[12]

- Pruritis
- Hypotension
- Angioedema
- Fever, chills
- Weakness, dizziness
- Erythematous rash on the face, neck, and upper torso
- Nausea, vomiting
- Tachycardia
- Rash on the extremities may occur but is typically less severe than the rash on the face, neck, and upper torso
- Chest or back pain, trunk muscle spasms

Diagnosis

VFS is diagnosed clinically and cannot be ruled out or confirmed by laboratory or other procedures. It's important to distinguish between serious cases and anaphylactic reactions caused by IgE [2].

It is important to distinguish between VFS and an anaphylactic reaction. Pruritus, an erythematous rash, and tachycardia are common features in both VFS and anaphylactic reactions. Stridor, angioedema, hives, and wheezing from bronchospasm are all symptoms of anaphylactic responses. IgE-mediated anaphylactic responses require prior exposure. VFS is a rate-related anaphylactoid adverse response that most frequently happens after receiving intravenous vancomycin for the first time [15].

Treatment/Management:

The intravenous antibiotic infusion needs to be discontinued right away if a patient develops VFS. It is necessary to provide supportive care. VFS is treated with H1 antihistamines

(diphenhydramine) and H2 antihistamines (cimetidine). Most of the time, future vancomycin doses can be administered at lower infusion rates [1].

Antihistamines such as cimetidine 300 mg intravenously and diphenhydramine 50 mg orally or intravenously can be used to treat minor cases (mild flushing and mild pruritus). Most episodes end in 20 minutes or less, at which point the vancomycin dose may be increased by 50%. Future doses should be administered over two hours at the new, slower rate [16].

Depending on their severity, moderate to severe cases (including those with a severe rash, hypotension, tachycardia, chest pain, back pain, muscular spasms, weakness, and angioedema) should be treated. Before assuming vancomycin flushing syndrome (VFS), patients with severe symptoms should be assessed for anaphylaxis or other serious causes of their symptoms. Antihistamines such as diphenhydramine and cimetidine can both be started intravenously if cautious examination reveals that the patient has VFS. Hypotension is treated with intravenous boluses of normal saline. The vancomycin can be continued and administered over four hours if the symptoms subside. Vancomycin alternatives should be utilized when they are available. If vancomycin must be continued, patients should receive diphenhydramine 50 mg intravenously and cimetidine 300 mg intravenously one hour before each dose, and vancomycin should be given over the course of four hours while being closely monitored.

If anaphylaxis symptoms, such as altered mental status, hypotension, stridor, difficulty breathing, wheezing, and hives, are present, treatment for anaphylaxis should be started right away, and the patient requires emergency care. The patient may have an epinephrine auto-injector with them that can be utilized, and epinephrine should be administered as soon as possible [16]. To speed up patient treatment and transfer to appropriate emergency care, emergency medical services should be activated immediately, if they are available.

Diphenhydramine and cimetidine may be used as a pre-treatment for patients who need a quick infusion of vancomycin. However, keeping infusion rates below 10 mg/min is the best preventive step to avoid VFS [18].

With appropriate care, the prognosis for people with VFS is excellent. Following a VFS incident, vancomycin may be taken once again. Guidelines for therapy and appropriate security measures should be followed. Hypotension should be treated with standard intravenous saline along with additional supportive care treatments [10].

Role of Clinical Pharmacist

- VFS is a typical side effect associated with the administration of intravenous vancomycin.
- There will probably be more VFS reactions as a result of the increased use of vancomycin.
- Healthcare professionals should be knowledgeable about this typical reaction, its symptoms, and how to handle cases when they arise.
- Vancomycin should not be infused quickly because this adverse drug reaction is frequently rate-related.
- Hospitals should set up infusion procedures to restrict vancomycin infusion rates to 1 gram/hour or slower at 10 mg/min.
- Ask patients if they have ever experienced any problems with vancomycin infusion to determine whether a patient needs pre-treatment for vancomycin as soon as possible.
- To reduce errors during ongoing transfusions, make sure there is ongoing observation of patient response to treatment and an appropriate handover at shift change.
- If you have any concerns about the patient's reaction to the drug or dose, speak with your supervisor or the doctor who recommended it.
- Understand the infusion protocols used at the healthcare center where they work.

Conclusion

Red man syndrome, also known as Vancomycin flushing syndrome (VFS), is an anaphylactoid reaction followed on by the fast infusion of the glycopeptide antibiotic vancomycin. It is characterized by the release of histamine from basophils and mast cells. Vancomycin use is more frequently associated with RMS. Therefore, the use of vancomycin should be known to healthcare providers. The likelihood of recovery or recurrence should increase with appropriate precautions and treatment guidelines.

Contributions

All authors contributed equally in the preparation of the manuscript.

Conflicts of interest

All authors show no conflicts of interest.

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