Int J Adv Life Sci Res. Volume 6(1)19-24
https://doi.org/10.31632/ijalsr.2023.v06i01.003

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org

Original Article

Vancomycin Hypersensitivity: Case Reports of Successful Vancomycin Desensitization

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Abstract

Background: Vancomycin infusion reaction (VIR, previously known as "red man syndrome") and anaphylaxis are two vancomycin hypersensitivity reactions with identical and clinically indistinguishable clinical presentations.

Method: This was a retrospective study where vancomycin hypersensitivity cases who underwent vancomycin desensitization in the past two years were recruited.

Results: Two vancomycin hypersensitivity cases were labelled as allergic to vancomycin in their previous hospitalizations before being admitted to our hospitals. The first case developed facial and lips swelling, while the second case developed transient hypotension; both occurred after the first dose of intravenous vancomycin, and hence were labelled as allergies without continuation of vancomycin in the previous hospitalizations. During current hospital admissions, both patients required vancomycin to treat infections. After weighing the risks and benefits, rapid vancomycin desensitization was conducted in both patients because of budget constraints in the public hospitals for alternative antibiotics. The desensitization was successfully conducted with no recurrence of previous reactions, and both cases completed intravenous vancomycin treatment for their infections.

Conclusion: Clinical presentations in VIR and anaphylaxis might be identical and indistinguishable, especially the reactions that have happened in the past and confirmatory allergy test is not available. Our study reported that vancomycin desensitization could be conducted in cases where VIR or anaphylaxis are uncertain, with the past reactions not life-threatening, and if no other alternative antibiotic can be used to treat infections.

Keywords:- Anaphylaxis, Desensitization, Vancomycin hypersensitivity, Vancomycin infusion reaction

Introduction

Vancomycin, a tricyclic glycopeptide antibiotic, is a bactericidal agent exhibiting activity against Gram-positive microorganisms by inhibiting their cell wall synthesis(Eyler & Shvets, 2019).Since its discovery in the 1950s, it has been widely used to treat infections caused by organisms resistant to certain antibiotics such as methicillin-resistant Staphylococcus aureus (MRSA), and as an alternative option in patients with allergy to penicillin group or cephalosporin group antibiotics(Levine, 2006,

Received on : 17th October 2022; Revised version received on :10th December 2022; Accepted: 23rd December 2022

2008).Vancomycin has unique pharmacokinetic/pharmacodynamic characteristics which can cause nephrotoxicity and ototoxicity; hence it requires frequent therapeutic drug monitoring to optimize its efficacy and minimize its toxicities(Levine, 2008). Newer antibiotics with better safety profiles and similar therapeutic effectiveness, such as linezolid, daptomycin, teicoplanin and ceftaroline might be preferred by the clinicians in certain cases(Paiva & Eggimann, 2017). However, these new alternative antibiotics might not be available in certain hospitals in low-to-middle-income countries like Malaysia due to budget constraints.

Vancomycin is known to induce two types of hypersensitivity reactions, the common vancomycin infusion reaction, VIR (previously known as red man syndrome), which ranges from 3.7% to 47% in infected patients, and the rare anaphylaxis with an unknown rate of occurrence(Wazny & Daghigh, 2001). VIR involves the flushing at the face, neck and upper torso, with a lesser extent of hypotension and angioedema. Itis caused by rapid (less than one hour) infusion of intravenous vancomycin, which is preventable and can be relieved with the administration of premedication like antihistamines(Sivagnanam & Deleu, 2003). However, anaphylaxis involves immunoglobulin and requires desensitization (Wazny & Daghigh, 2001). Previously reported cases requiring vancomycin desensitization were clear-cut vancomycin hypersensitivity reactions of VIR and/or anaphylaxis. (Chopra et al., 2000; Kitazawa et al., 2006; Kupstaitė et al., 2010; Lerner & Dwyer, 1984; Lin, 1990; Sorensen et al., 1998; Wong et al., 1994) However, infrequent, identical but clinically indistinguishable presentations of vancomycin hypersensitivity reactions might cause uncertainty among physicians and pharmacists in deciding whether desensitization is required, especially in cases with no other alternative antibiotic available for the treatment of infections and confirmatory allergy testing is unavailable at the facility. In this paper, we reported two cases of vancomycin hypersensitivity presented with infrequent clinical presentation of VIR, with vancomycin desensitization being conducted successfully using the rapid protocol.

Case 1

A 65-year-old Malay lady with underlying type 2 diabetes mellitus, hypertension, end-stage renal disease(ESRD) with intermittenthemodialysis and lumbar spondylosis was admitted with the chief complaint of fever for two days. She also had lethargy, vomiting and loose stool prior to the admission. Both central and peripheral blood cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA), which was sensitive to vancomycin, trimethoprim-sulfamethoxazole, gentamicin, linezolid and rifampicin; resistant to penicillin, erythromycin, ciprofloxacin, oxacillin and fusidic acid. The diagnosis of MRSA catheter-related bloodstream infection (CRBSI) was made. However, she was noted to have an allergy reaction to vancomycin in her previous admission, which was about six months ago. During the previous admission, she was also diagnosed with MRSA CRBSI, and intravenous vancomycin was started. After administering the first dose of vancomycin, she developed facial and lips swelling, with no erythematous rash or other signs of reactions. According to the guidelines, vancomycin is the first-line antibiotic for the treatment of MRSA bacteraemia, and daptomycin can be used as an alternative antibiotic (Brown et al., 2021; Liu et al., 2011). However, daptomycin was not available in our hospital. Hence linezolid was used in her treatment. The reactions subsided slowly after two days and an allergy card was issued to her. She completed two weeks of linezolid from the culture clearance and was discharged well.

During this admission, intravenous vancomycin was reconsidered as the treatment choice because of the unaffordable higher treatment cost of linezolid and longer antibiotic duration was expected due to recurrent MRSA CRBSI with deep-seated abscess. Upon further investigation, the patient’s previous reactions were suspected to be not a true allergy. Hence, vancomycin desensitization was conducted without recurrence of any similar reactions, and she completed almost three months of intravenous vancomycin due to complicated MRSA CRBSI. In the following six months, she was admitted twice and received intravenous vancomycin in both admissions without any issues. No desensitization was required in her subsequent treatments.

Case 2

A 62-year-old Malay lady with underlying type 2 diabetes mellitus, hypertension and ESRD on intermittenthemodialysis, complained of on-and-off fever for one week. Both central and peripheral blood cultures grew methicillin-resistant coagulase negative *Staphylococcus* (MRCoNS), which was sensitive to vancomycin only and resistant to penicillin, erythromycin, oxacillin and fusidic acid. Impression of MRCoNS CRBSI was made. She had a history of anaphylactic reaction to vancomycin at a different hospital few years ago and received an allergy card. As she was unsure about the allergy history, a call was made to that hospital to clarify and further investigate the allergy reaction. It was found that after completing the first dose of intravenous vancomycin infusion, she complained of dizziness, with blood pressure lowered to 88/46 mmHg, without flushing, shortness of breath, facial, lips and eyes swelling. Intravenous vancomycin was then discontinued, and an allergy card was issued to her. As there was no other alternative available to treat MRCoNS, vancomycin desensitization was conducted. The process was carried out successfully, and she completed the treatment of vancomycin without any similar issues.

Discussions

Both VIR and anaphylaxis are vancomycin hypersensitivity reactions with identical and clinically indistinguishable presentations(Wazny & Daghigh, 2001). VIR involves the release of histamine from mast cells, while anaphylaxis is immunoglobulin E-mediated (Ig-E)(Kupstaitė et al., 2010; Wazny & Daghigh, 2001).The differences between these two types of vancomycin hypersensitivity are presented in Table 1.

Table 1. Differences between the two types of vancomycin hypersensitivity (Kupstaitė et al., 2010; Wazny & Daghigh, 2001).

	Vancomycin Infusion Reaction (VIR)	**Anaphylaxis**
Involve mast cell activation	Yes	No
Mediated by immunoglobulin-E	No	Yes
Infusion rate dependent	Yes	No
When will occur	Usually at first dose, also at any time.	Occurs in patients who become sensitized to vancomycin.
Mechanisms	Mast cells and basophils from the skin, lung, gastrointestinal tract, myocardium, and vascular system release histamine.	Patient sensitized to vancomycin will produce vancomycin-specific Ig-E. Repetitive vancomycin administrations result in cross-linking of Ig-E receptors on the sensitized mast cells, causing them to release vasoactive mediators, and such reactions are amplified by cytokines.
Presentations	• The severity of the reaction depends on the amount of histamine released. • Generalized flushing, pruritus, rash; hypotension, chest pain, and dyspnea have been reported in more severe reactions. • Hypotension without a rash has been reported.	• The early phase: local edema, smooth muscle contraction, vasodilatation, and increased permeability of postcapillary venules. • The late phase: involves the recruitment and activation of basophils, eosinophils, and other cell types, and may persist for 48 hours. • The inflammatory cascade is life-threatening unless medical

		treatment is immediately obtained.
Strategies to prevent occurrence	• Reducing vancomycin infusion rate to not exceeding 10 mg/min relieves the symptoms of RMS. • Premedication with IV/oral antihistamines and corticosteroids prior to vancomycin infusion.	• Not to re-administer vancomycin during anaphylaxis, as it may cause respiratory arrest. • Antihistamines and corticosteroids do not reverse the acute reactions but can be used to alleviate or prevent the occurrence of late reactions (urticaria, hypotension, or recurrent bronchospasm).
Indication of vancomycin desensitization	Usually not required, except in RMS that develops despite using the preventive measures	• Yes

In Malaysia, vancomycin is readily available in most public hospitals but alternative antibiotics such as linezolid and daptomycin might not be readily available in public hospitals without infectious disease specialty due to budget constraints. Because of the difference in price and unavailability of alternative antibiotics, vancomycin desensitization was decided. Cases of successful vancomycin desensitization in ESRD patients with severe anaphylactic reactions have been reported(Chopra et al., 2000; Sorensen et al., 1998).From the literature search, two vancomycin desensitization protocols were commonly used; one is a rapid protocol that can be completed in four hours if repetition of infusion is not required, while the other is a slow protocol which takes up to 13 days to complete(Lin, 1990). As the slow protocol may induce organism resistance, it is recommended to be used in patients who develop hypersensitivity during the rapid protocol(Kitazawa et al., 2006).

Table 2. Rapid vancomycin desensitization protocol (Lerner & Dwyer, 1984; Wazny & Daghigh, 2001)

Premedication Diphenhydramine 50 mg iv and hydrocortisone 100 mg iv 15 minutes prior to initiation of protocol, then q6h throughout protocol.

Infusion No.	Dilution	Vancomycin Dose (mg)	Concentration (mg/mL)
1	1:10 000	0.02	0.0002
2	1:1000	0.20	0.002
3	1:100	2.0	0.02
4	1:10	20	0.2
5	Standard	500	2.0

Preparation

1. Prepare a standard bag of 500 mg vancomycin in 250 mL NS or D5W; label as infusion no. 5, vancomycin 2 mg/mL.
2. Draw up 10 mL of the standard vancomycin 2-mg/mL preparation and place in 100-mL bag of NS or D5W; label as infusion no. 4, vancomycin 0.2 mg/mL.
3. Draw up 10 mL of the 0.2-mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 3, vancomycin 0.02 mg/mL.
4. Draw up 10 mL of the 0.02 mg/mL solution and place in a 100-mL bag of NS or D5W; label as infusion no. 2, vancomycin 0.002 mg/mL.
5. Draw up 10 mL of the 0.002-mg/mL solution and place in a 100- mL bag of NS or D5W; label as infusion no. 1, vancomycin 0.0002 mg/mL.

Infusion Rate Directions

Initiate infusion rate at 0.5 mL/min (30 mL/h) and increase by 0.5 mL/min (30 mL/h) as tolerated every 5 min to a maximum rate of 5 mL/min (300 mL/h). If pruritus, hypotension, rash, or difficulty breathing occurs, stop infusion and reinfuse the previously tolerated infusion at the highest tolerated rate. This step may be repeated up to three times for any given concentration.

Upon completion of infusion no. 5, immediately administer the required dose of vancomycin in the usual dilution of NS or D5W over 2hours. Decrease rate if the patient becomes symptomatic or,alternatively, increase rate if the patient tolerates the dose. Administer diphenhydramine 50 mg po 60 min prior to each dose.

D5W = dextrose 5% in water; NS = NaCl 0.9%.

As a result, the rapid vancomycin desensitization protocol with premedication antihistamine and corticosteroid by Lerner & Dwyer was referred (Table 2) (Lerner & Dwyer, 1984; Wazny & Daghigh, 2001). Intravenous diphenhydramine 50 mg was replaced with intravenous chlorpheniramine 10 mg in our protocol, as intravenous diphenhydramine was unavailable in our hospital.

The desensitization was conducted successfully in both cases with no hypersensitivity reactions observed. Both cases successfully completed the intravenous vancomycin for at least 14 days at the standard infusion rate recommended by the manufacturer.

Conclusions

Although different mechanisms are involved in the two different vancomycin hypersensitivity reactions, identical non-specific clinical presentations are clinically indistinguishable. Therefore, physicians and pharmacists should be aware of the infrequent vancomycin hypersensitivity reactions and the management. Furthermore, in cases of uncertainty and risk of rechallenge, vancomycin desensitization should be made well-known among the physicians and pharmacists, as it may provide an option to the patients and clinicians, especially in hospitals with resource limitation and no other choices for the new generation of antibiotics.

Conflict of Interest

The authors have no conflicts of interest to declare with regard to the content of this article.

Ethics Statement

This study was registered in National Medical Research Register (NMRR), Malaysia (NMRR ID-22-00715-NRA). Ethical waiver was informed by the NMRR secretariat.

Acknowledgment

The authors would like to thank the Director General of Health, Malaysia, for his permission to publish this manuscript. The authors would also like to thank the Hospital Director of Hospital Tuanku Ampuan Najihah, Dr. Sarina Sidek, and the Head of Pharmacy Department, Madam Nur Azlin Adam, for their support in preparing this manuscript.

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