Annals of Clinical and Medical Case Reports

Case Series

ISSN 2639-8109 | Volume 6

The Incidence Rate of Vancomycin-Induced Thrombocytopenia in Orthopedics: A Single-Center Retrospective Case Series

Wang L, Qi L*, Jiang Y, Zhang S and Li M

Department of Orthopaedic Surgery, Qilu Hospital of Shandong University, No.107, Wenhua Xi Road, Jinan, Shandong, 250012, China

***Corresponding author:**

Lei Qi,
Department of Orthopaedic Surgery,
Qilu Hospital of Shandong University,
No.107, Wenhua Xi Road, Jinan, Shandong,
250012, China, Tel: 86-0531-82166531,
Fax: 86-0531-82166535
Email: qilei_spine@hotmail.com

Received: 08 Feb 2021
Accepted: 26 Feb 2021
Published: 01 Mar 2021

Citation:

Qi L. The Incidence Rate of Vancomycin-Induced Thrombocytopenia in Orthopedics: A Single-Center Retrospective Case Series. Ann Clin Med Case Rep. 2021; V6(1): 1-5

Keywords:

Vancomycin; Thrombocytopenia; Orthopedics; Adverse effect; Antibiotic

1. Abstract

1.1. Objective: Vancomycin has been an indispensable alternative for the treatment of severe and complicated infections, especially in orthopedics department. However, as a severe adverse drug effect, vancomycin-induced thrombocytopenia (VIT) has not attracted enough attention. The objective of the research was to analyze the incidence rate of VIT in orthopedic patients.

1.2. Methods: The medical records of inpatients receiving intravenous vancomycin medication from January 2015 to December 2020 in a single center of orthopedics department were retrospectively reviewed. The gender, age, diagnosis, duration of vancomycin usage and changes of platelet counts were collected to analyze the occurrence of VIT and its incidence rate.

1.3. Results: A total of 258 cases receiving intravenous vancomycin medication (≥3 days) were enrolled in the study. The mean age was 57.3 years and the mean duration of vancomycin usage was 11.2 days. There were 141 cases in the treatment group and 117 cases in the prevention group. The changes of platelet counts were recorded and reviewed carefully. VIT was diagnosed in 2 patients, which were both in treatment group. The incidence rate of VIT in orthopedics was 0.78%.

1.4. Conclusion: Whenever acute thrombocytopenia occurs without a known cause in patients receiving vancomycin medication, VIT should be considered. This is the first clinical report of VIT and incidence rate in orthopedics. Although the incidence rate of VIT in orthopedics was 0.78% in our research, the clinical rare adverse effect should also attract enough attention and close monitoring.

2. Introduction

Vancomycin is a glycopeptide antibiotic with activity against most Gram-positive microorganisms. It prevents the formation of peptidoglycans of the bacterial cellular wall and inhibits the growth of bacteria [1]. Since developed in 1956, Vancomycin was widely used for the treatment of different severe infections caused by Gram-positive bacteria and in patients allergic to penicillin. Nowadays, Vancomycin has been an indispensable alternative for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) and penicillin-resistant Streptococcus [2].

However, the adverse effect related to vancomycin should not be neglected. Vancomycin-induced thrombocytopenia (VIT) was first reported in 1985 and was further explained in the published case reports [3]. Thrombocytopenia is strongly associated with poor clinical outcomes, illness severity, the development of multiple organ failure, the length of hospital stays and mortality.

Vancomycin has been widely used in the orthopedics department because of the high incidence of device-associated infections, mostly due to coagulase-negative staphylococci and other organisms that are sensitive only to vancomycin [4]. However, the real incidence rate and details of VIT in orthopedics remains unknown. In the current study, we retrospectively reviewed the records of inpatients using intravenous vancomycin in a single orthopedics center and analyzed the incidence rate of VIT.

3. Methods

3.1. Subjects

The study was approved by the ethics committee of Qilu Hospital of Shandong University. We retrospectively reviewed the records of inpatient population received intravenous vancomycin medication between January 2015 and December 2020 in the Department of Orthopaedic Surgery of Qilu Hospital of Shandong University. Patients who met any of the following criteria at the start of therapy were excluded: platelet count of <150 X 10^9/L; hematological diseases; diagnosis of disseminated intravascular clotting or severe sepsis; received anticancer or immunosuppressive drugs within 4 weeks; vancomycin medication duration of <3 days; and insufficient clinical data.

The following available information was collected retrospectively from medical records: gender, age, diagnosis, duration of vancomycin medication, changes of platelet count. According to the details of bacteria culture and disease, the usage of vancomycin was divided into treatment and prevention subgroups. Treatment medication refers to positive bacterial culture or definite infectious disease but without or with negative bacterial culture. Prevention medication refers to suspicious infection without or with negative bacterial culture. The diagnosis of all the cases was either joint or spine disease. According to the specialty, the cases were divided into Joint and Spine subgroups.

3.2 Diagnosis of VIT

There are no standard diagnostic criteria for VIT. According to the literature search, the diagnosis of VIT in the current study was established based on the clinical criteria, including the following items [5]: platelet count <100 X 10^9/L for consecutive 3 times, the drop of platelet count should exclude the reason of dilution, including anemia; the vancomycin use must precede the onset of thrombocytopenia; recovery from thrombocytopenia must be complete and sustained after the vancomycin is discontinued; other causes of thrombocytopenia must be excluded, including severe sepsis, DIC and heparin. The laboratory testing for vancomycin-induced antiplatelet antibodies was not readily accessible in our hospital.

3.3 Statistical Analysis

Means were calculated for age, drug medication time. Differences of medication duration between subgroups were determined by the *t*-test. P≤0.05 was considered as statistically significant. Statistical measures were performed using Statistical Package for Social Science (SPSS, 19.0).

4. Results

4.1 Patients Population

The present study was composed of a group of 258 patients receiving intravenous vancomycin medication (123 male and 135 female). The patients' characteristics were summarized in Table 1. The mean age was 57.3 years. All the cases received the intravenous vancomycin medication with 1g q12h. There were 141 cases in treatment group and 117 cases in prevention group. The mean age was 58.0 and 54.2 years for treatment and prevention subgroups respectively. According to the specialty, there were 137 cases of joint and 121 of spine diseases. The mean duration of vancomycin medication was 11.2 days for all 258 cases. The cases in treatment group received longer medication than prevention group (14.8 versus 6.9 days, P<0.05).

Table 1: Characteristics of the cases receiving intravenous vancomycin

	All the cases	Treatment Group	Prevention Group
Number of cases (n)	258	141	117
Sex（M/F）(n)	123 / 135	74 / 67	49 / 68
Age（yr）	53.6（14-86）	58.0（14-86）	54.2（15-79）
Specialty （Joint/Spine） (n)	137 / 121	76 / 65	61 / 56
Duration of medication（d）	11.2（3-51）	14.8（3-51）	6.9（3-24）

4.2 Incidence rate of VIT

Among all the 258 cases, there were 2 cases suffering from thrombocytopenia during the vancomycin medication period and was diagnosed as VIT. The incidence rate of VIT in patients from orthopedics department was 0.78%. All the 2 cases were in treatment medication groups. One was surgical site infection after lumbar fusion surgery and another was hip joint infection. For the treatment medication, the incidence rate of VIT was 1.42%. The nadir platelet count was 2 X 10^9/L and 29 X 10^9/L for the two cases. The time from the vancomycin use to platelet count dropping to nadir was 15 and 12 days respectively. After the discontinuation of vancomycin, the time of platelet reaching to normal was 15 and 8 days respectively.

4.3 Details of the two VIT cases

Case 1

A 79 years old male patient was admitted to the ward due to progressive low back pain after posterior lumbar fusion surgery. About 5 months ago, he received posterior lumbar decompression, L4-5 intervertebral fusion and internal fixation due to lumbar degenerative spondylolisthesis. He complained of progressive low back pain, without other symptoms, including fever, pain and numbness of legs. The initial body temperature was 36.5^{0}C. CRP and ESR was 87.65 mg/L and 47 mm/h respectively. For the medical history, he suffered from type 2 diabetes and took metformin to control the blood glucose. According to the radiological results and high level of inflammation index, postoperative infection of lumbar fusion was diagnosed. His initial platelet count was 187 X 10^9/L. The empirical treatment of intravenous vancomycin 1g q12h was used for consecutive 15 days. Meanwhile, NSAIDs were prescribed to alleviate low back pain. On day 12, the patient

received revision surgery. The bacterial culture of tissue attained during surgery showed Staphylococcus Epidermidis infection, which was sensitive to vancomycin. The patient's platelet count dropped to 12 X 10^9/L on day 13 and the nadir of 2 X 10^9/L on day 15. The discontinuation of vancomycin use was made on day 15. The patient received 10U platelet transfusion totally from day 15 to 19. The platelet count began to increase and increased to 208 X 10^9/L on day 30 (Figure 1). However, the patient did not show and bleeding symptoms and signs. During the treatment, he did not receive other drugs which may cause thrombocytopenia, including heparin. The infection was controlled and improved progressively. CRP and ESR was 39.05 mg/L and 4 mm/h respectively when the patient discharged from the hospital. The diagnosis of VIT was made during the treatment and the patient recovered well finally.

Case 2

A 73 years old male patient was admitted to the ward due to the pain and dysfunction of left hip and was diagnosed with left hip joint infection. The mobility of left hip joint was restricted seriously and Patrick sign examination could not be performed. He did not suffer from fever and other chronic diseases. The initial body temperature was 36.5^{0}C. CRP and ESR was 101.43 mg/L and 120 mm/h respectively. He received the joint puncture and biopsy, which showed Staphylococcus Epidermidis infection. Then, intravenous vancomycin 1g q12h was used for consecutive 12 days. His initial platelet count was 211 X 10^9/L and dropped to 29 X10^9/L on day 12. The vancomycin use was discontinued immediately. The platelet count increased to 153 X 10^9/L on day 20. (Figure 2) The level of CRP and ESR dropped to 38.29 mg/L and 30 mm/h respectively.

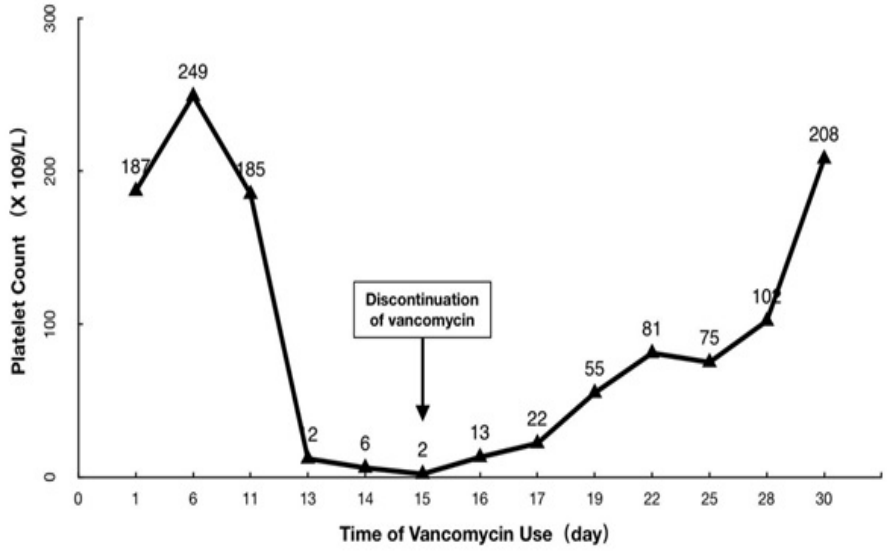

Figure 1: The changes of patient's platelet count for case 1

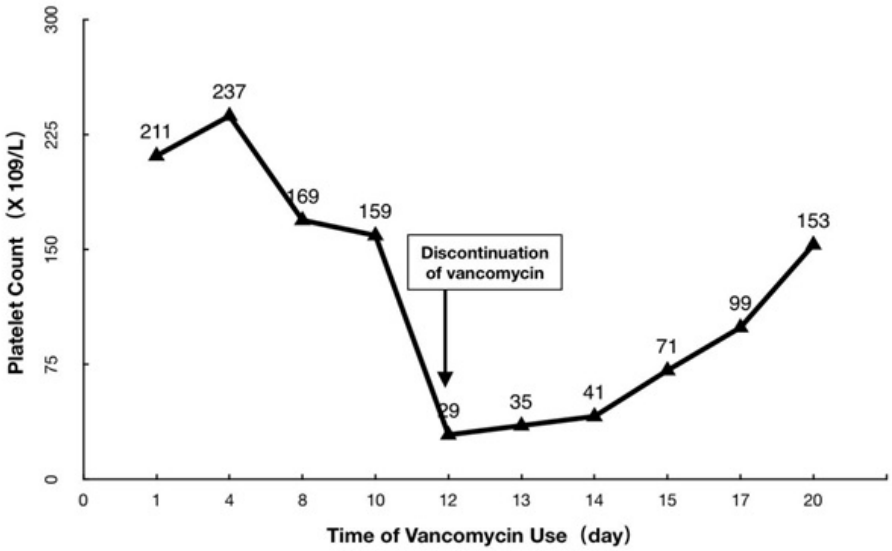

Figure 2: The changes of patient's platelet count for case 2

5. Discussion

Vancomycin is recommended intravenously as a treatment for severe and complicated infections and is the most common antibiotic agent used against perioperative infections when no other antibiotic was available. The high incidence of device-associated infections further popularized the usage of vancomycin. These bacteria are implicated in infections resulting from biomedical devices, such as cardiac valve, pacemakers, neurosurgical devices, orthopedic implants, and vascular catheters [4]. Especially in the orthopedics department, most of the spine and joint surgeries are involved with implants, including spinal pedicle screw and joint prosthesis [6]. In addition, perioperative spine and joint infections usually cause disastrous results and eradication of these infections requires long-term therapy for a duration of vancomycin usage of 6-8 weeks [7].

Drug-induced thrombocytopenia (DIT) has been reported as an adverse reaction of over 300 medications. It is normally present 5 to 10 days after the initial exposition to the drug, or within hours after the secondary exposition to a drug that has been used in a previous occasion [8]. DIT can be caused by three mechanisms: direct toxic effect, hapten formation and the innocent-bystander immune response [9]. Vancomycin is an established cause of DIT, especially in acutely ill, hospitalized or elderly patients. The pathogenesis of VIT is not well understood. Hapten-dependent antibody formation is the most cited mechanism for VIT. It is postulated that vancomycin binding to platelet glycoproteins induces the generation of antibodies, which are attached to the drug-platelet complex and cause platelet lysis [10]. However, as for how vancomycin causes antibody production and how antibodies precipitate the destruction of platelet structure and loss of platelet function, the detailed aspects remain unknown. Towhid et al. demonstrated that vancomycin exposure indeed leads to platelet activation and apoptosis [11].

The definition of thrombocytopenia is inconsistent in literatures. Generally, thrombocytopenia is defined as a platelet count below 100 X 10^9/L, which may occur due to the decelerated production of platelets, caused by bone marrow toxicity, or increased destruction of platelets mediated by the immune response [12]. It is deemed to be severe when the platelet count drops below 10 X 10^9/L, rendering the patient with an increased risk of bleeding [13]. One third of the patients with VIT experienced severe bleeding with a mean platelet count of 8.4 X 10^9/L, while the mean platelet count was 35 X 10^9/L in asymptomatic patients with VIT [10]. However, some patients with severe thrombocytopenia have no bleeding symptoms, including the two VIT cases in the current study, even when the platelet count dropped to 2 X 10^9/L.

VIT is not depended on cumulative doses, and seems to be a duration-dependent reaction [10]. Drygalski reported that the nadir platelet count was reached about 8 days after treatment with vancomycin was initiated, and the mean nadir platelet count was 13.6 X 10^9/L (1 X 10^9-60 X 10^9) [14]. However, for the case of re-exposure of vancomycin, interval before VIT may be significantly shorter. Another characteristic of VIT is transfusion resistance. Previous research reported that platelet counts did not rise significantly in 78% of patients after platelet transfusions. The survival time of infused platelets is reduced significantly because of immune response and the transfusion of platelets does not always result in expected increases in platelet count. However, if severe thrombocytopenia and bleeding occur, transfusion is also recommended.

The incidence rate of VIT remained unknown and varied based on patient population. Until now, most of the reports of VIT were case reports and there were only several studies used different definitions for VIT. A study performed in a university hospital in Brazil in 2011 revealed that the prevalence of the adverse effects of vancomycin is 27.6% and the incidence rate of thrombocytopenia (platelet count <100 X 10^9/L) was 7.1% [15]. Wunderink et al. reported that thrombocytopenia (platelet count <150 X 10^9/L, if normal at baseline, or a 50% decrease, if low at baseline) occurred in 13.2% of vancomycin-treated pneumonia patients [16]. In our research, the incidence rate of VIT is 0.78% for all cases and 1.4% for treatment cases, which was much lower than two studied above, which may because the clinical criteria for the diagnosis of VIT were much more stringent.

Currently, there is not a universally accepted gold standard for the diagnosis of DIT including vancomycin. Early diagnosis may be made through detection of vancomycin-dependent IgG or IgM antiplatelet antibodies [14]. However, laboratory testing for these antibodies is not readily accessible and test methods are not standardized. Moreover, the true sensitivity of these tests is not clear. Some research suggested that antibodies are only detectable after a minimum of 10 days from initiating the treatment [17, 18].

Although testing for vancomycin-induced antiplatelet antibodies is the most elucidated diagnostic alternative, clinical findings cannot be underestimated in patients presenting thrombocytopenia and the associated use of vancomycin [8]. Although laboratory tests for detecting special antibodies were not performed for the cases in our research, the clinical manifestations help make the diagnosis of VIT. The recovery of platelet count after discontinuation of the drug is also a strong proof of VIT.

Immediate discontinuation of drug was regarded as the most important action, which should be made base on the patients' clinical status. The platelet count generally starts to rise within 1 to 2 days thereafter [17]. In most cases, gradual resolution of VIT occurs about 5 to 7 days after discontinuation of vancomycin [14, 19]. For the cases with renal deficiency, VIT may last longer because of delayed drug clearance. If the VIT or bleeding persists longer, treatment with corticosteroids, intravenous immunoglobulins, or even plasm exchange could be considered. In addition, the patients with confirmed VIT should avoid future exposure to vancomycin. Vancomycin-induced antibodies may exist for months after

cessation of vancomycin therapy and several cases of recurrent thrombocytopenia following vancomycin rechallenge have been reported [20].

As for VIT, a different diagnosis should not be overlooked. Thrombocytopenia could be caused by several different conditions such as sepsis, DIC and large blood loss. Vancomycin is often clinically overlooked as a cause of thrombocytopenia, especially in a scenario of sepsis. In our research, thrombocytopenia caused by sepsis could be excluded due to the regression in the clinical signs of inflammation, reduction of laboratorial ESR and CRP.

In addition, the Naranjo Adverse Drug Reaction Probability Scale is recommended by the World Health Organization and the Ministry of Health, being perhaps the most widely accepted instrument for assessment of causality for adverse drug reaction [21]. The algorithm yields a score of 6 for vancomycin, indicating that VIT was probable in our patients.

6. Conclusion

In conclusion, whenever an acute thrombocytopenia occurs without a known cause in patients receiving medication with vancomycin, VIT should be considered. Diagnosis is often challenging because of concurrent contribution factors and a lack of a definite diagnostic criteria. Early diagnosis of VIT is crucial as it leads to timely discontinuation of the drug, avoidance of unnecessary treatment and prevention of severe bleeding events. This is the first clinical report of VIT and incidence rate in orthopedics. Although the incidence rate of VIT in orthopedics we reported was 0.78%, the clinical rare adverse effect could cause serious consequences and should also attract enough attention and close monitoring. More related researches are needed in future to further the VIT and relevant issues.

7. Funding: This work was supported by China Postdoctoral Science Foundation Grant (No.2019M650165) and National Natural Science Foundation of China (No. 81902276).

References

1. Jeffres MN. The Whole Price of Vancomycin: Toxicities, Troughs, and Time. Drugs. 2017; 77: 1143-54.
2. Rubinstein E, Keynan Y. Vancomycin revisited - 60 years later. Front Public Health. 2014; 2: 217.
3. Walker RW, Heaton A. Thrombocytopenia due to vancomycin. Lancet. 1985; 1: 932.
4. Thushara RM, Hemshekhar M, Kemparaju K, Rangappa KS, Devaraja S, Girish KS. Therapeutic drug-induced platelet apoptosis: an overlooked issue in pharmacotoxicology. Arch Toxicol. 2014; 88: 185-98.
5. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med. 1998; 129: 886-90.
6. Anemüller R, Belden K, Brause B, Citak M, Del PJL, Frommelt L, et al. Hip and Knee Section, Treatment, Antimicrobials: Proceedings of International Consensus on Orthopedic Infections. J Arthroplasty. 2019; 34: S463-463S475.
7. Rao N, Ziran BH, Wagener MM, Santa ER, Yu VL. Similar hematologic effects of long-term linezolid and vancomycin therapy in a prospective observational study of patients with orthopedic infections. Clin Infect Dis. 2004; 38: 1058-64.
8. Danieletto CF, Ferreira GZ, Farah GJ, Cuman RK. Vancomycin-induced thrombocytopenia: a rare adverse effect in a patient -submitted to bone graft in the jaw. Spec Care Dentist. 2017; 37: 38-42.
9. Marraffa J, Guharoy R, Duggan D, Rose F, Nazeer S. Vancomycin-induced thrombocytopenia: a case proven with rechallenge. Pharmacotherapy. 2003; 23: 1195-8.
10. Mohammadi M, Jahangard-Rafsanjani Z, Sarayani A, Hadjibabaei M, Taghizadeh-Ghehi M. Vancomycin-Induced Thrombocytopenia: A Narrative Review. Drug Saf. 2017; 40:4 9-59.
11. Towhid ST, Schmidt EM, Tolios A, Münzer P, Schmid E, Borst O, et al. Stimulation of platelet death by vancomycin. Cell Physiol Biochem. 2013; 31: 102-12.
12. van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf. 2004; 27: 1243-52.
13. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. J Thromb Haemost. 2009; 7: 911-8.
14. Von Drygalski A, Curtis BR, Bougie DW, McFarland JG, Ahl S, Limbu I, et al. Vancomycin-induced immune thrombocytopenia. N Engl J Med 2007; 356: 904-10.
15. Marinho DS, Huf G, Ferreira BL, Castro H, Rodrigues CR, de Sousa VP, et al. The study of vancomycin use and its adverse reactions associated to patients of a Brazilian university hospital. BMC Res Notes. 2011; 4: 236.
16. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, et al. Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis. 2012; 54: 621-9.
17. Arnold DM, Kukaswadia S, Nazi I, Esmail A, Dewar L, Smith JW, et al. A systematic evaluation of laboratory testing for drug-induced immune thrombocytopenia. J Thromb Haemost. 2013; 11: 169-76.
18. Ganly P, Downing J, Stiven P, Frizelle F, Badami K. Clinical and serological diagnoses of a patient with vancomycin-induced thrombocytopenia. Transfus Med. 2011; 21: 137-9.
19. Rowland SP, Rankin I, Sheth H. Vancomycin-induced thrombocytopaenia in a patient with severe pancreatitis. BMJ Case Rep. 2013; 2013: bcr2013200830.
20. Lobo N, Ejiofor K, Thurairaja R, Khan MS. Life-threatening haematuria caused by vancomycin-induced thrombocytopenia. BMJ Case Rep. 2015; 2015.
21. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30: 239-45.