Severe thrombocytopenia caused by vancomycin in the intensive care unit: a case report and systematic review

Guanru Wang[1], Xiao-Xiao LI[2], Qing-gang Ge[1], Chao Li[1], Na He[1], Peng Yao[3], Chuhui Wang[1], Min Yi[1], Zongyu Wang[1], Luwen Shi[3], and Rongsheng Zhao[1]

[1]Peking University Third Hospital
[2]Affiliation not available
[3]Peking University School of Pharmaceutical Sciences

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Abstract

Thrombocytopenia can cause substantial morbidity and mortality in critically ill patients. There are multiple etiology factors and various mechanisms associated with thrombocytopenia, of which drug-induced thrombocytopenia (DITP) deserves attention. Herein, we describe a case of severe thrombocytopenia during intensive care unit (ICU) hospitalization that was probable to be associated with vancomycin. In addition, clinical studies evaluating thrombocytopenia caused by vancomycin were systematically reviewed and 6 studies with acceptable quality were included and analyzed. By revealing the process of identifying this case of DITP and reviewing relevant clinical studies, a risk alert of vancomycin related severe hematotoxicity should be focused on.

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Guanru Wang [1a, 2+], Xiaoxiao Li [1a, 2+], Qinggang Ge[1b], Chao Li [1b], Na He [1a,2], Peng Yao [2], Chuhui Wang[1a, 2], Min Yi [1b], Zongyu Wang[1b], Luwen Shi [2*], and Rongsheng Zhao[1a, 2*]

1 a Department of Pharmacy, b Department of Intensive Care Unit, Peking University Third Hospital, Beijing 100191, China

2 Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

*Correspondence: Lu-wen Shi MHPE, Email: Shilu@bjmu.edu.cn, Add: 38 Xueyuan Rd., Haidian District, Beijing, P. R. China (100191), Tel: 86-10-82265740

Rong-sheng Zhao Ph.D., Email: zhaorongsheng@bjmu.edu.cn, Add: 49 North Garden Rd., Haidian District, Beijing, P. R. China (100191), Tel: 86-10-82265810

+ These authors contributed equally to this work.

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Abstract : Thrombocytopenia can cause substantial morbidity and mortality in critically ill patients. There are multiple etiology factors and various mechanisms associated with thrombocytopenia, of which drug-

induced thrombocytopenia (DITP) deserves attention. Herein, we describe a case of severe thrombocytopenia during intensive care unit (ICU) hospitalization that was probable to be associated with vancomycin. In addition, clinical studies evaluating thrombocy-topenia caused by vancomycin were systematically reviewed and 6 studies with acceptable quality were included and analyzed. By revealing the process of identifying this case of DITP and re-viewing relevant clinical studies, a risk alert of vancomycin related severe hematotoxicity should be focused on.

Keywords: Vancomycin; thrombocytopenia; adverse drug reaction; critically illness; systematic review

Thrombocytopenia is defined as a platelet count below the lower limit of normal (<150 $\times$ 10^9/L for adults). Degrees of thrombocytopenia can be further subdivided into mild (100 $\times$ 10^9/L to 150 $\times$ 10^9/L), moderate (5 $\times$ 10^9/L to 9.9 $\times$ 10^9/L), and severe (under 5 $\times$ 10^9/L). In the setting of immune thrombocytopenia, a platelet count <3 $\times$ 10^9/L is considered to represent severe thrombocytopenia.[1] Thrombocytopenia can cause substantial morbidity and mortality in critically ill patients. The incidence of thrombocytopenia in adult critically ill patients can reach 8.3% to 67.6%.[2] Meanwhile, thrombocytopenia is associated to significantly increased bleeding and blood transfusion and even mortality events.[3,4]

There are multiple etiology factors and various mechanisms that can cause thrombocytopenia, and clinical decision-making is quite complicated. Common causes of thrombocytopenia are bone marrow suppression, primary hematological diseases, autoimmune diseases, severe infections and medications. As an increasingly cause of isolated thrombocytopenia, drug-induced thrombocytopenia (DITP) can be attributed to foods and herbal remedies besides medications.[5]Among the intensive care unit (ICU) patients with new-onset thrombocytopenia, medications cause can account for 16%.[6] DITP is an important clinical problem for physicians, of which drug-dependent anti-body-mediated platelet destruction is one of the main mechanisms. The most implicated medications include quinine, sulfamethoxazole, penicillin and linezolid, etc.[7] Vancomycin is used for gram-positive cocci infections, especially in methicillin-resistant staphylococcus aureus (MRSA) infection.[8] Severe renal impairment, hypersensitivity reactions and infusion-related reactions caused by vancomycin have been widely recognized in clinical practice, while adverse reactions such as agranulocytosis and thrombocytopenia are rare and can easily be ignored.

Herein, we present a case with probable vancomycin-induced severe thrombocytopenia during ICU hospitalization. We aim to provide evidence-based references for the diagnosis and treatment of vancomycin-induced thrombocytopenia in critically ill patients.

Case Report

A 64-year-old male patient was admitted to hospital on April 21st, 2021 (Day 1, hereafter referred as D1) with 3-day-paroxysmal abdominal cramps, accompanied by diarrhea, nausea as well as vomiting. The diagnosis was transverse colon perforation on admission, with rectal mass, septic shock and hypokalemia. An emergency surgery was performed to repair laparotomy perforation as well as radical treatment of rectal cancer. After the operation, he was transferred to intensive care unit (ICU) (D1). The score of the sequential organ failure assessment[9], acute physiology and chronic health evaluation[10], and Richmond agitation-sedation scale[11] was 8, 19 and -2 scores, respectively. For surviving sepsis, ICU physicians implemented bundle strategies as antimicrobial therapy (imipenem and cilastatin sodium for injection, 0.5g q6h), fluid resuscitation (20% human albumin, 40g; crystoloid solution, 3000ml) and sedation therapy (remifentanil, propofol, midazolam).

During the ICU hospitalization (D1-D9), his blood routine examinations, body temperature, and procalcitonin are shown in Table 1. On D2, vancomycin (1g, q12h) was administrated intravenously combined with imipenem and cilastatin sodium, due to an operative recording showing a serious fecal contamination in his abdominal cavity. Unexpectedly, his platelets count (7 $\times$ 10^9/L) severely decreased on D4 (Figure 1). According to the blood routine test (Table 1) and medical history, we roughly excluded common blood diseases and autoimmune diseases. Meanwhile, hepatic failure and disseminated intravascular coagulation (DIC) were put aside. Thus, idiopathic thrombocytopenic purpura (ITP) was a major concern which might be caused by infection or medications, etc. After transfusion of platelets (1 U) and blood cells (2 U) on D4, his platelets count recovered a little (26 $\times$ 10^9/L). However, it went down again in the morning of D5

(14×10^9/L). The severe infection, as the first factor suspected to thrombocytopenia was alleviating at the same moment. Among all the medication used between D1-D5, vancomycin aroused suspicion and was discontinued (with its trough concentration being as 11 ug/ml). And a platelet transfusion (1U) was given to prevent hemorrhage.

In the evening of D5, as the body temperature increased to 38.7, the patient had to re-administered vancomycin. As a result, his platelets count was reduced from 61 x 10^9/L to 3 x 10^9/L within 8 hours. He had to receive a platelets (2U) transfusion again in the morning of D6. As drainage fluid culture suggested only Escherichia Coli (ESBL-) infection, we completely discontinued vancomycin but kept on imipenem and cilastatin sodium. The platelets count backed to 135 x 10^9/L on D7 and never dropped again since then. He was transferred back to the general ward after being extubated (D9). On D14, he stopped using antibiotics and was discharged with a better health condition. According to the Naranjo adverse reaction evaluation scale (Table 2)[12], the total score was 6, and the relationship between vancomycin and thrombocytopenia was judged as "probably".

Literature Review

We systematically searched PubMed, Embase, and the Cochrane Library, with two keywords vancomycin AND thrombocytopenia to start the search. Clinical studies that evaluated thrombocytopenia caused by vancomycin, without limitation to patients or controlled drugs. Papers written in languages other English were excluded. Published reviews, case report, conference abstracts and non-clinical studies were also excluded. The reviewer (WGR) assessed publications for eligibility. Any paper with uncertainty in regard to inclusion or exclusion was discussed between 3 authors (WGR, LXX and ZRS) until a consensus of opinion was reached. Newcastle-Ottawa Scale (NOS) quality evaluation scale and JBI checklist for analytical cross sectional studies were used to evaluate the quality of included studies. [19,20] For each study, both the process of data extraction and quality evaluation were performed by one author (WGR) using predesigned tables, followed by the check of another author (LXX). Any disagreement was resolved by discussion among all authors (WGR, LXX and ZRS).

Overall, 600 articles were retrieved. After reviewing the titles, abstracts and full texts, the reviewers agreed on a final selection of 6 studies for inclusion. The screening flow chart is presented in Figure 2, with the basic information of the six studies included shown in table 3. Of these, 5 studies were identified as retrospective cohort with a controlled drugs as linezolid.[13-17] One was a cross-section study with a single-arm.[18] The patients were mainly adults with bacterial infection, and the duration treatment (vancomycin or linezolid) was more than 7 days. Regarding quality assessment, 5 cohort studies were identified as high quality (score 7-8) based on NOS tool[13-17], 1 cross section study as medium quality (score 5) based on JBI tool.[18] All studies were therefore acceptable in this review.

We reviewed the frequency, severity and occurrence of bleeding events due to thrombocytopenia caused by vancomycin or linezolid (Table 4 and Figure 2). Only one study showed that the frequency of thrombocytopenia (defined as [?] 30 % decrease in platelets) caused by linezolid in patients was significantly higher than that caused by vancomycin (OR = 3.38, 95 % CI: 1.87–6.08).[17] Five studies showed that vancomycin and linezolid had no significant difference in thrombocytopenia (either defined as platelets¡150 x 10^9/L or¡100 x 10^9/L). As shown in Figure 3, the meta-analysis of the two studies showed that vancomycin and linezolid had no significant difference in thrombocytopenia (defined as platelets<150 x 10^9/L, RR=1.01, 95%CI=0.64-1.58).[14-15] The cross-section study showed that the incidence of vancomycin-induced thrombocytopenia (defined as platelets<100 x 10^9/L) was 7.1 %.[18] Although no life-threatening bleeding events was reported to occur, vancomycin-induced thrombocytopenia can be as low as less than half of the baseline platelets of patients. The above results suggested that the incidence and severity of thrombocytopenia caused by vancomycin should be paid attention.

Discussion

DITP diagnosis is complicated owing to multiple causes of acquired thrombocytopenia in ICU patients. Among thrombocytopenic patients who present with severe infection, DITP is a very important distinction

to make. Firstly, we roughly excluded primary blood diseases and autoimmune diseases through medical history and laboratory examination results. Then we focused on the infection and medication factors. As a priority factor suspected to thrombocytopenia, the severe infection had been alleviating (Table 1) while PLT decreased. Thus, vancomycin caught our attention. It offered further clinical evidence as thrombocytopenia appeared when vancomycin was re-administered, and disappeared as vancomycin discontinued.

Thrombocytopenia was occurred in 7.1 % patients treated with vancomycin[18], however, it could be easily overlooked as its description and incidence have not been labelled. There were some case reports of vancomycin-induced thrombocytopenia before. Back in 1985, Walker presented a 48-year-old female patient with secondary peritonitis after peritoneal dialysis. During the treatment period, vancomycin (500mg, i.v.gtt.) was given first, followed by intraperitoneal injection of 120 mg/day, and the patient showed a significant thrombocytopenia 6 days later.[21] Howard reported in 1997 that a 58-year-old male patient admitted to hospital due to osteomyelitis caused by MRSA, who manifested thrombocytopenia after vancomycin administration.[22] In 2013, a systematic review including pediatric patients (<18 years old)[23] found that 32 substances had potential pathogenic effects in thrombocytopenia, including vancomycin (in 3 of 21 cases). In 2017, 30 case reports with 30 patients were included in a scoping review reported vancomycin-induced thrombocytopenia.[24] It can occur on the 1st to 10th days after drug exposure. The time window for the platelet count dropping to the lowest point ranged from 4 hours to 10 days after drug exposure. The median platelet count was often dropping $< 20 \times 10^9/L$[25,26], with those $<2 \times 10^6/L$ to $1 \times 10^8/L$ occurred bleeding.[27] The degree and occurring time (the time for the platelet count to drop to $7 \times 10^9/L$ was 2 days of vancomycin use) of thrombocytopenia in our case was basically consistent with the previous reports.

Significantly, it shows that vancomycin causing thrombocytopenia by accelerating platelet destruction via drug-dependent platelet reactive antibodies. Compared with linezolid, another agent commonly used for MRSA, vancomycin-induced immunemediated thrombocytopenia occurs more rapidly, while linezolid-induced mye-losuppression-mediated thrombocytopenia occurs for a longer time (usually 2 weeks).[28] Previous experience showed that the incidence of thrombocytopenia caused by linezolid was high. Notably, based on our systematic review, there was no significant difference in leading thrombocytopenia (defined as platelets$<150 \times 10^9/L$) between vancomycin and linezolid (RR=1.01, 95%CI=0.64-1.58).

Usually, DITP was alleviative after vancomycin withdrawal, with the severe one required platelet infusion.[24] There is no evidence for the efficacy of immunosuppression in treating DITP. In previous reports, vancomycin was discontinued in 29 of 30 patients, and platelet counts in 17 patients recovered within 5-6 days.[25, 26] In this process, patients' infection control needs to be taken into account when discontinuing vancomycin. In our case, luckily, the patient was definitely infected with Escherichia Coli, and we decisively discontinued vancomycin after thrombocytopenia was observed again. As thrombocytopenia leads to an increased risk of bleeding, the transfusion of platelets was a common management though it did not always result in expected increases in platelet counts of affected patients (67% transfusion resistant of 20 patients).[24] In this case, platelet infusion was given when platelet count was at $8 \times 10^9/L$ and $14 \times 10^9/L$, and platelet 2U infusion was given at $3 \times 10^9/L$.

There are some limitations in this study. Firstly, only postoperative drainage fluid was collected for culture specimens after starting antimicrobial therapy, but no blood samples obtained before at emergency. We should continue to improve the implementation of sepsis bundle, emphasizing the importance of retaining blood samples to monitor and analyze the bacteria before the empirical antibiotic treatment.[27] Secondly, we couldn't confirm whether the cause was DITP or not, as our hospital doesn't perform tests of drug-dependent platelet reactive antibodies.[29] In order to better identify DITP and improve patient prognosis, it is suggested to improve the accessibility of platelet reactive antibody technology in the future. Thirdly, only three major databases were searched for systematic reviewed, therefore some literatures might be overlooked.

Conclusions

In this study, we report a patient with probable vancomycin-induced severe thrombocytopenia during ICU hospitalization. By revealing the process of identifying this case of DITP and systematic reviewing relevant

clinical studies, a risk alert of vancomycin related severe hematotoxicity should be focused on.

Author Contributions:

All authors took part in the final version for submission and accept overall accountability for ac-curacy and integrity of the manuscript.

WGR:Data curation, writing - original draft

LXX: Conceptualization, investigation, writing - original draft

GQG: Conceptualization

LC: Conceptualization, writing - review & editing

HN: Conceptualization, writing - review & editing

YP:Writing - review & editing

WCH: Writing - review & editing

YM: Investigation

WZY: Investigation

SLW: Supervision, validation

ZRS: Supervision, validation

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Table 1 Body temperature, blood routine examinations and procalcitonin (D1-D9) [+]

Date	Tmax[++] ()	Red blood count (10^{12}/L)	White blood count (10^9/L)	Platelet count (10^9/L)	Neutrophil (10^9/L)	Procalcitonin (ng/ml)
D1	38.3	4.82	3.99	287	3.09	98.3
D2	38.8	3.4	12.08	212	11.41	69.63
D3	38.0	3.17	2.28	109	1.95	43.67
D4	37.8	2.91	10.21	7-26[§]	9.55	17.64
D5	38.7	3.44	6.89	14-61[§]	5.58	10.87
D6	37.4	3.64	7.49	3-99[§]	6.12	4.81
D7	37.8	3.32	8.81	135	6.96	2.92
D8	37.9	3.32	9.30	225	7.78	1.76
D9	37.1	3.57	11.96	265	10.75	/

+ Blood sampling was generally 4:00-6:00 am, platelets count was retested within 30 minutes of finishing platelets transfusion.

++ Maximum body temperature of the day

§ "-" represents changes after platelet infusion

Table 2 Naranjo adverse drug reaction probability scale

Questions	**Scores**	**Scor**
	Yes	**No**
1. Are there previous conclusive reports on this reaction?	+1	0
2. Did adverse event appear after the suspected drug was given?	+2	-1
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0
4. Did the adverse reaction appear when the drug was readministered?	+2	-1
5. Are there alternative causes that could have caused the reaction?	-1	+2
6. Did the reaction reappear when a placebo was given?	-1	+1
7. Was the drug detected in any body fluid in toxic concentrations?	+1	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0
10. Was the adverse event confirmed by any objective evidence?	+1	0
Total score		

First Author Year	Study type	Treatments	Patient populations	Patient populations	Sample size	Duration of treatment (Days)
			Underlying diseases	Age		
Zhou-2020[13]	Retrospective cohort study	Linezolid	Acute myeloid leukaemia (AML) and bacterial infection	45.8 ± 13.6	36	[?] 7
		Vancomycin		47.2 ± 13.1	41	

First Author Year	Study type	Treatments	Patient populations	Patient populations	Sample size	Duration of treatment (Days)
Nalini-2004[14]	Retrospective cohort study	Linezolid	Gram-positive bacterial orthopedic infections	NM	20	Mean 71
		Vancomycin		NM	52	Mean 42
Stanley-2003[15]	Retrospective cohort study	Linezolid	Nosocomial pneumonia	58.7% [?]65	356	Mean 10.7±4.4
		Vancomycin		51.9% [?]65	330	Mean 10.5±3.7
Nimish-2012[16]	Retrospective cohort study	Linezolid	Bacterial infection	68.5 ± 12.4	251	Mean 10
		Vancomycin		68.6 ± 13.3	251	Mean 7
Satoshi-2013[17]	Retrospective cohort study	Linezolid	Severe infections	68.0±15.4	91	7.0±5.8
		Vancomycin		64.0±14.1	160	10.0±11.4
Daniel-2011[18]	Cross-sectional study	Vancomycin	Bacterial infection	50.6	98	9.7(95%CI: 8.0-11.7)

Table 3 Basic characteristics of included studies

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