

ORIGINAL ARTICLE

Vancomycin-Induced Immune Thrombocytopenia

Annette Von Drygalski, M.D., Brian R. Curtis, M.S., Daniel W. Bougie, Ph.D., Janice G. McFarland, M.D., Scott Ahl, B.S., Indra Limbu, M.D., Kelty R. Baker, M.D., and Richard H. Aster, M.D.

ABSTRACT

BACKGROUND

From the Department of Medicine, Medical College of Wisconsin (A.V.D., I.L., R.H.A.), and the Blood Research Institute, BloodCenter of Wisconsin (B.R.C., D.W.B., J.G.M., S.A., R.H.A.) — both in Milwaukee; and the Department of Medicine, Baylor College of Medicine, Houston (K.R.B.). Address reprint requests to Dr. Aster at the Blood Research Institute, BloodCenter of Wisconsin, 8727 Watertown Plank Rd., Milwaukee, WI 53226, or at richard.aster@bcw.edu.

Vancomycin has only rarely been implicated as a cause of thrombocytopenia, and there is only limited evidence that this complication is caused by immune mechanisms. We conducted a study to determine whether thrombocytopenia is caused by vancomycin-dependent antibodies in patients being treated with vancomycin.

METHODS

We identified and characterized vancomycin-dependent, platelet-reactive antibodies in patients who had been referred for testing during a 5-year period because of a clinical suspicion of vancomycin-induced thrombocytopenia. We obtained clinical information about the patients from their referring physicians.

RESULTS

Drug-dependent, platelet-reactive antibodies of the IgG class, the IgM class, or both were identified in 34 patients, and clinical follow-up information was obtained from 29 of these patients. The mean nadir platelet count in these patients was 13,600 per cubic millimeter, and severe bleeding occurred in 10 patients (34%). Platelet levels returned to baseline in all 26 surviving patients after vancomycin was stopped. In 15 patients, the drug was continued for 1 to 14 days while other possible causes of thrombocytopenia were investigated. Vancomycin-dependent antibodies were not found in 25 patients who had been given vancomycin and in whom thrombocytopenia did not develop.

CONCLUSIONS

Severe bleeding can occur in patients with vancomycin-induced immune thrombocytopenia. The detection of vancomycin-dependent antiplatelet antibodies in patients receiving the antibiotic in whom thrombocytopenia develops, and the absence of antibodies in patients given the drug in whom platelet counts remain stable, indicate that these antibodies are the cause of the thrombocytopenia.

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MANY MEDICATIONS CAN INDUCE ANTIBODIES that cause thrombocytopenia.^{1,2} Neutropenia is a well-recognized complication of therapy with vancomycin, a glycopeptide antibiotic widely used for the treatment of bacterial infections that are resistant to other agents.³⁻⁵ However, we have found reports of only 12 cases of thrombocytopenia associated with exposure to this agent,⁶⁻⁹ and there is only limited evidence for an immune mechanism underlying the thrombocytopenia.^{6,7} Patients receiving vancomycin may have life-threatening bacterial sepsis and are often given heparin; vancomycin may not be considered as the cause of thrombocytopenia in such patients because both sepsis and treatment with heparin are frequently associated with thrombocytopenia.¹⁰⁻¹²

In this report, we summarize clinical and laboratory findings in 29 patients in whom thrombocytopenia developed while they were receiving vancomycin, and we present evidence that this complication was caused by vancomycin-dependent, platelet-reactive antibodies. Our observations indicate that vancomycin-induced immune thrombocytopenia can cause life-threatening bleeding in an acutely ill patient being treated with this antibiotic and that vancomycin as a cause of thrombocytopenia can be overlooked.

METHODS

PATIENTS

From 2001 through 2005, serum samples from patients in several parts of the United States in whom vancomycin-induced thrombocytopenia was suspected were referred to the Platelet and Neutrophil Immunology Laboratory at the BloodCenter of Wisconsin (Milwaukee) to be tested for vancomycin-dependent antibodies. Information about the hospital course of antibody-positive patients was obtained from their referring physicians and by one of the authors, who was directly involved in the care of six of the patients. Serum samples from 25 patients who were treated with vancomycin for at least 6 days and in whom thrombocytopenia did not develop were obtained at the Froedtert Memorial Lutheran Hospital, in Milwaukee. The institutional review boards of the BloodCenter of Wisconsin and the Froedtert Memorial Lutheran Hospital approved the study.

DETECTION OF DRUG-DEPENDENT ANTIBODIES

Drug-dependent, platelet-reactive antibodies were detected by flow cytometry according to previously described methods.¹³ Each patient sample was tested against normal platelets in the presence and absence (control) of vancomycin, 0.3 mg per milliliter. After the samples had been washed in buffer containing vancomycin at the same concentration as that in the primary mixture, platelet-bound immunoglobulins were detected with a fluorescein-labeled anti-immunoglobulin reagent. A positive reaction was defined as one in which the increase in the mean fluorescence intensity of platelets after vancomycin therapy was at least twice that in control serum samples. Reactions of this degree always exceeded control values by at least 3 SD. The optimal concentration of vancomycin for the detection of vancomycin-dependent antibodies was 0.3 mg per milliliter; higher concentrations of vancomycin caused nonspecific binding of IgG to platelets.

RESULTS

SEROLOGIC FINDINGS

Vancomycin-dependent, platelet-reactive antibodies of the IgG class, IgM class, or both were detected in 34 patients (about 20% of the samples referred for testing). Follow-up clinical information was obtained from 29 patients (mean age, 66 years; range, 37 to 87), of whom 15 were men. Twenty-three patients had been given the antibiotic for treatment of *Staphylococcus aureus* infections, three for fever of unknown origin, and three for prophylaxis against postsurgical infection.

Figure 1 shows the clinical course of a representative case of vancomycin-induced thrombocytopenia in a 69-year-old woman with staphylococcal osteomyelitis after a surgical procedure. Figure 2 is a representative assay showing a vancomycin-dependent antibody. Of the 29 patients for whom follow-up information was available, 16 had only IgG antibodies, 3 had only IgM antibodies, and 10 had both IgG and IgM antibodies. Figure 3 compares the reactions of serum samples from these patients with those of samples from 25 patients who were given vancomycin but did not have thrombocytopenia. No vancomycin-dependent antibodies were detected in any of the 10 patients with quinine-induced thrombocytopenia

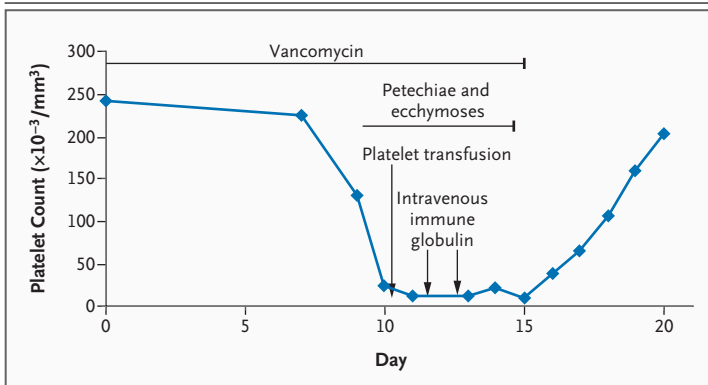


Figure 1. Clinical Course of a Patient with Vancomycin-Induced Thrombocytopenia.

After 10 days of vancomycin therapy, thrombocytopenia and bleeding developed in a 69-year-old woman who had staphylococcal osteomyelitis after a surgical procedure. A platelet transfusion failed to raise the platelet count. Two infusions of intravenous immune globulin were given because of the suspicion that the patient might have had post-transfusion purpura or autoimmune thrombocytopenia. Vancomycin was discontinued on day 15.

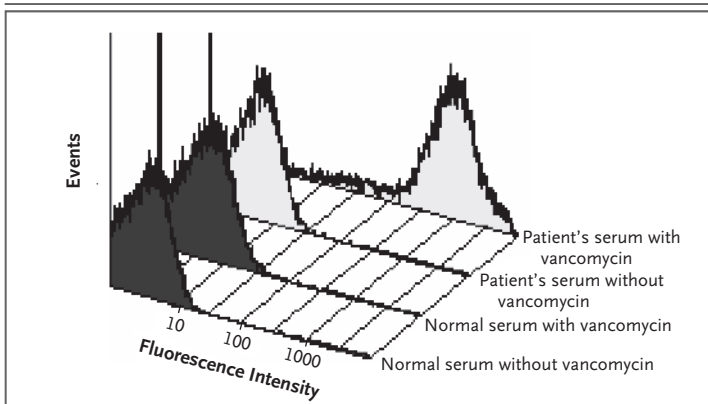


Figure 2. Serum Samples from a Patient with Thrombocytopenia and from a Normal Donor Reacting against Platelets, as Measured by Flow Cytometry.

Binding of an IgG antibody was detected when the patient's serum was tested in the presence of vancomycin at a concentration of 0.3 mg per milliliter, but no reaction occurred in the absence of vancomycin. No reaction was detected when normal serum was tested, whether or not vancomycin was present. Fluorescence intensity was measured in arbitrary units.

(data not shown). No IgG antibodies and only a single example of an IgM vancomycin-dependent antibody were detected in blood from 451 normal donors (253 men and 198 women) ranging in age from 17 to 73 years. The patients with vancomycin-dependent antibodies had been exposed to a total of at least 35 medications other than vanco-

mycin and heparin. No platelet-reactive antibodies specific to any of these drugs were identified in these patients.

When serum samples from patients with thrombocytopenia were tested for vancomycin-dependent antibodies with the use of platelets from a patient with type I Glanzmann's thrombasthenia that lacked glycoprotein IIb/IIIa, 12 of 22 samples did not show a reaction. This result indicates that the antibodies are probably specific for glycoprotein IIb/IIIa ($\alpha_{IIb}\beta_3$ integrin) alone. Six serum samples reacted both with platelets from the patient with Glanzmann's thrombasthenia and with normal platelets; however, the reaction against the platelets from the patient with Glanzmann's thrombasthenia was less strong, a result suggesting that the antibodies recognize glycoprotein IIb/IIIa and at least one other platelet glycoprotein. Four samples reacted equally strongly against both types of platelets, a result indicating specificity for glycoproteins other than glycoprotein IIb/IIIa. Specificity for glycoprotein IIb/IIIa was confirmed by the modified antigen-capture enzyme-linked immunosorbent assay (ELISA)¹⁴ in two serum samples that did not show a reaction with platelets from the patient with Glanzmann's thrombasthenia.

PLATELET COUNTS

In patients with vancomycin-dependent antibodies, the platelet levels dropped by a mean of 93% from pretreatment values (range, 76 to 99%) while they were receiving vancomycin (Table 1). On average, the nadir platelet count was reached about 8 days after treatment with vancomycin was initiated (range, 1 to 27), and the mean nadir platelet count was 13,600 per cubic millimeter (range, 1000 to 60,000). After vancomycin was discontinued, the platelet level returned to baseline in all patients except three who died from complications of sepsis. The median time required for the platelet level to return to at least 150,000 per cubic millimeter after vancomycin was stopped was 7.5 days (range, 4.0 to 17.0).

BLEEDING

Ten patients (34%) had severe bleeding characterized by florid petechial hemorrhages, ecchymoses, and oozing from the buccal mucosa (described as "wet purpura" in seven patients). Of these 10 patients, 1 had gross hematuria, 2 had lower gas-

trointestinal hemorrhages requiring transfusion, 2 had intrapulmonary hemorrhages, and 2 had excessive bleeding from venepuncture sites. Of the remaining 19 patients, 10 had petechial hemorrhages and ecchymoses, and 9 had no clinically significant bleeding. The mean platelet count in 10 patients with severe bleeding was 8400 per cubic millimeter (median, 4000; range, 1000 to 24,000). The mean fluorescent signal given by the antibodies in these patients was significantly greater than that in patients with mild or no bleeding ($P=0.01$). The mean platelet count in the nine asymptomatic patients was 35,000 per cubic millimeter (median, 20,000; range, 10,000 to 60,000).

HEPARIN EXPOSURE

A diagnosis of heparin-induced thrombocytopenia was considered in 10 of the 29 antibody-positive patients. Two patients, one of whom had thrombosis, had had a previous episode of heparin-induced thrombocytopenia associated with a strongly positive human platelet factor 4 (PF4) ELISA test and return of platelet levels to normal after heparin was stopped. However, these two patients began vancomycin treatment more than 1 week after heparin was discontinued, when platelet counts were normal. The PF4 ELISA test was negative in the other eight patients, which made the diagnosis of heparin-induced thrombocytopenia unlikely.¹² A PF4 ELISA test¹⁵ performed at a later date on stored serum samples was weakly positive in six other patients. Of 25 patients who were given vancomycin without the consequent development of thrombocytopenia, 3 had weakly positive PF4 ELISA tests. Positive PF4 ELISA tests are not unusual in acutely ill patients given heparin and, in themselves, are not diagnostic of heparin-induced thrombocytopenia.^{12,16}

ALTERNATIVE DIAGNOSES

In 14 patients, vancomycin was discontinued shortly after thrombocytopenia was detected. In the other 15, vancomycin was continued for 1 to 14 days (median, 3). In these patients, the low platelet count was initially attributed to heparin-induced thrombocytopenia (eight patients), autoimmune thrombocytopenia (five patients), or post-transfusion purpura (two patients), and therapeutic measures appropriate for these conditions were instituted. Subsequent studies failed to support these diagnoses and, in each patient, there was no clinically

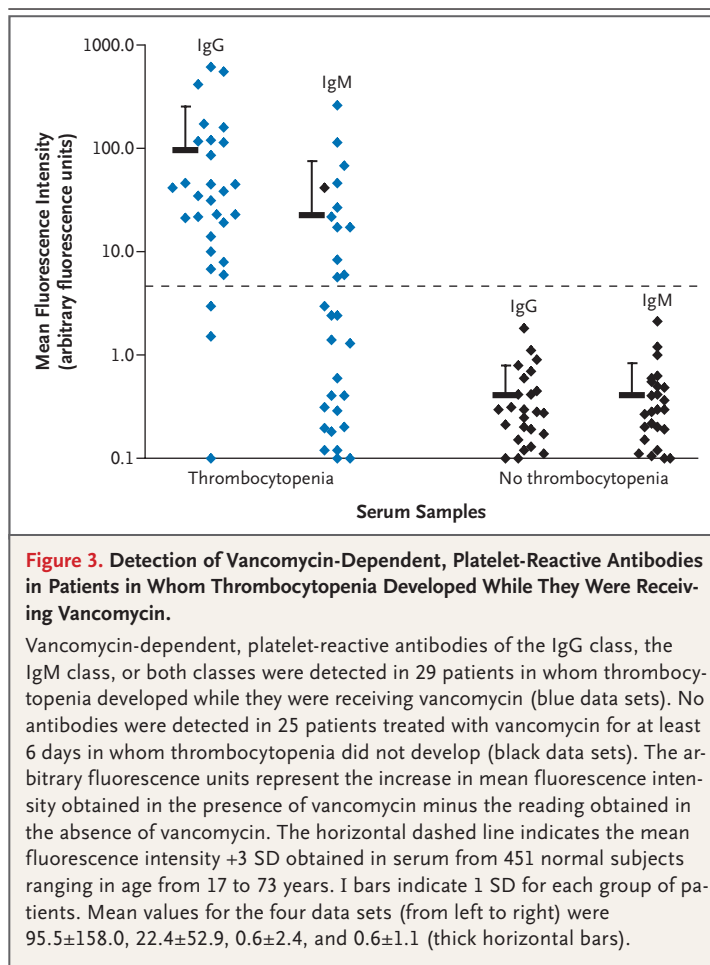


Figure 3. Detection of Vancomycin-Dependent, Platelet-Reactive Antibodies in Patients in Whom Thrombocytopenia Developed While They Were Receiving Vancomycin.

Vancomycin-dependent, platelet-reactive antibodies of the IgG class, the IgM class, or both classes were detected in 29 patients in whom thrombocytopenia developed while they were receiving vancomycin (blue data sets). No antibodies were detected in 25 patients treated with vancomycin for at least 6 days in whom thrombocytopenia did not develop (black data sets). The arbitrary fluorescence units represent the increase in mean fluorescence intensity obtained in the presence of vancomycin minus the reading obtained in the absence of vancomycin. The horizontal dashed line indicates the mean fluorescence intensity +3 SD obtained in serum from 451 normal subjects ranging in age from 17 to 73 years. I bars indicate 1 SD for each group of patients. Mean values for the four data sets (from left to right) were 95.5 ± 158.0 , 22.4 ± 52.9 , 0.6 ± 2.4 , and 0.6 ± 1.1 (thick horizontal bars).

significantly increase in the platelet count until vancomycin was discontinued.

ACUTE THROMBOCYTOPENIA SHORTLY AFTER INITIATION OF VANCOMYCIN

In three patients with no known history of exposure to vancomycin, acute, severe thrombocytopenia developed within 24 hours after the initiation of an infusion of vancomycin. Two of the patients had had multiple surgeries at other institutions and might have been given the drug in connection with these procedures. Two other patients in whom thrombocytopenia developed within 1 day after the initiation of treatment had had a previous episode of vancomycin-associated thrombocytopenia, one 2 weeks earlier and the other 6 months earlier. It is likely that these cases of thrombocytopenia were caused by antibodies persisting from a previous episode of vancomycin-induced thrombocytopenia.

Table 1. Platelet Levels in Patients with Vancomycin-Dependent Antibodies.

Variable	Nadir Platelet Count		Percentage Decrease in Platelet Count from Baseline (N=29)	Days Required for Platelet Count to Return to 150,000/mm ³ after Discontinuation of Vancomycin (N=25)*
	No. of Days after Initiation of Vancomycin (N=24)†	Count per mm ³ (N=29)		
Mean	8.3	13,600	93	7.2
Median	7.0	10,000	95	7.5
Range	3.0–27.0	1,000–60,000	76–99	4.0–17.0

* Information about the number of days was not available for 1 of the 26 surviving patients.

† Data from five patients in whom thrombocytopenia developed immediately after treatment are excluded.

PROLONGED THROMBOCYTOPENIA IN PATIENTS WITH RENAL INSUFFICIENCY

Three patients with impaired renal function, two of whom were undergoing dialysis, remained profoundly thrombocytopenic (platelet count, <20,000 per cubic millimeter) for 7 to 8 days after vancomycin was discontinued. In one, residual vancomycin was detected in a plasma sample drawn 6 days after the antibiotic was stopped. Persistent, severe thrombocytopenia in these patients may have resulted from slow clearance of the drug due to renal insufficiency.¹⁷

DEATHS

Three patients died from complications of staphylococcal infection 7, 8, and 13 days after vancomycin was started, and 1, 2, and 7 days, respectively, after the onset of thrombocytopenia. All had platelet counts of less than 10,000 per cubic millimeter at the time of death. Two had intrapulmonary hemorrhages, but the extent to which this contributed to their deaths was uncertain.

FOLLOW-UP ON ANTIBODY-NEGATIVE PATIENTS

Vancomycin was ruled out as the cause of thrombocytopenia in 8 of 10 patients who had thrombocytopenia with no detectable vancomycin-dependent antibodies; it was ruled out because the thrombocytopenia was present before vancomycin was started, the patient did not actually have thrombocytopenia (the test was ordered by mistake), or the platelet level returned to normal while the patient was still receiving vancomycin. For three patients, there were convincing alternative explanations for low platelet levels: two had disseminated intravascular coagulation and one had

well-documented heparin-induced thrombocytopenia. However, in two patients, severe thrombocytopenia (platelet count, <30,000 per cubic millimeter) developed 4 and 6 days after vancomycin was started; the platelet level returned to normal after the antibiotic was stopped, and there was no associated condition that could explain the thrombocytopenia.

TREATMENT

Fourteen patients received one or more platelet transfusions during the acute phase of thrombocytopenia. In 11 of these patients, no clinically significant rise in platelets was detected 6 to 24 hours later. In the other three patients, information was inadequate to determine whether there was a response to platelet transfusions. Five patients were given corticosteroids, three were given one or more courses of intravenous immune globulin, two were treated with plasma exchange, and one was given anti-Rh immune globulin, all on the assumption that they had autoimmune thrombocytopenia or post-transfusion purpura. No clinically significant rise in the platelet level occurred in these patients until vancomycin was discontinued.

DISCUSSION

All 29 patients in whom vancomycin-dependent antibodies were detected had been exposed to the drug — most for at least 6 days, a time sufficient to mount an immune response to the drug — before thrombocytopenia developed. The platelet levels returned to pretreatment values in all 26 survivors after vancomycin was discontinued.

In two patients, an immediate, severe drop in

platelet levels occurred on inadvertent rechallenge with vancomycin after recovery of the platelet count. A diagnosis of heparin-induced thrombocytopenia was considered for 10 patients, but the timing of heparin exposure, negative assays for heparin-induced thrombocytopenia antibodies, and the severity of the thrombocytopenia made it unlikely that heparin contributed to the drop in platelet levels.^{12,16,18} No vancomycin-dependent antibodies were detected in 25 patients who had normal platelet counts after receiving vancomycin for at least 6 days or in 10 patients with quinine-induced thrombocytopenia. A vancomycin-dependent antibody was detected in only 1 of 451 normal subjects. Follow-up observations of 10 patients with thrombocytopenia and with negative tests for vancomycin-dependent antibodies provided evidence that vancomycin was not responsible for thrombocytopenia in at least 8 of the patients.

Together, these observations constitute evidence that vancomycin-induced antibodies were the cause of the thrombocytopenia in the 29 patients we studied and indicate that the test we used is specific for vancomycin-dependent antiplatelet antibodies. A recent report indicates that teicoplanin, a glycopeptide antibiotic used in Europe, can also cause immune thrombocytopenia.¹⁹

The vancomycin-dependent antibodies we detected behaved like antibodies from patients with thrombocytopenia induced by quinine and other drugs.^{20,21} The antibodies reacted with platelets only in the presence of vancomycin, and 12 of 22 serum samples required platelet membrane glycoprotein IIb/IIIa for the reaction.²⁰ In contrast to a hapten-specific antibody,^{22,23} binding of this type of drug-dependent antibody does not require covalent linkage of the drug to the target molecule.^{21,23} The molecular basis of the drug-dependent binding of such antibodies to the platelet is, however, unknown.^{23,24}

Several features of vancomycin-induced thrombocytopenia are notable. One third of the patients

had extensive ecchymoses and hemorrhage ("wet purpura"). Bleeding of this severity is unusual in patients with thrombocytopenia induced by other drugs, even when the platelet count is very low.^{13,25,26} Platelet transfusions failed to elevate platelet levels in 11 of 14 patients. Experience with a patient who had two episodes of severe thrombocytopenia 6 months apart indicates that vancomycin-induced antibodies can persist for months in the absence of exposure to vancomycin. Detection of a vancomycin-dependent antibody in 1 of 451 normal subjects raises the possibility that on rare occasions, naturally occurring antibodies may cause acute thrombocytopenia after a single dose of vancomycin, which appears to have occurred in 1 patient in this study. Thrombocytopenia in patients with renal failure can persist for a week or more after discontinuation of vancomycin, presumably because clearance of the antibiotic is delayed.

Because the size of the vancomycin-treated population from which our samples were obtained is unknown, we are unable to estimate the frequency with which vancomycin causes immune thrombocytopenia. The diagnosis of drug-induced thrombocytopenia is often overlooked, even in patients who present with acute, severe thrombocytopenia after exposure to quinine, which is a well-recognized cause of the disorder.^{27,28} In our study, treatment was implemented for alternative diagnoses while vancomycin was continued in about half the patients. We conclude that testing for drug-dependent antibodies can be helpful in identifying the cause of thrombocytopenia in patients who are receiving vancomycin.

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Dr. Aster reports providing free scientific advice to the Platelet and Neutrophil Immunology Laboratory at the BloodCenter of Wisconsin, which performs diagnostic testing on patients suspected of having drug-induced immune thrombocytopenia; Mr. Curtis is the paid supervisor of this laboratory. No other potential conflict of interest relevant to this article was reported.

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