Henry Ford Hospital Medical Journal

Volume 37 | Number 1 Article 8

3-1989

Quinidine-Induced Immune Thrombocytopenia

Mansoor N. Saleh

Nadhav Dhodaphar

Karen Allen

Albert F. LoBuglio

Quinidine-Induced Immune Thrombocytopenia

Mansoor N. Saleh, MD,* Nadhav Dhodaphar, MD,† Karen Allen,‡ and Albert F. LoBuglio, MD§

We have identified six cases of quinidine-induced immune thrombocytopenia based on clinical evidence and in association with elevated amounts of platelet surface IgG. The degree of thrombocytopenia did not correlate with severity of clinical symptoms, nor did it predict the amount of IgG on the platelet surface. Three of the patients recovered promptly after drug discontinuation alone whereas the other patients received additional corticosteroid therapy. The clinical presentation, mode of diagnosis, and therapeutic considerations in the treatment of drug-induced thrombocytopenia are discussed. (Henry Ford Hosp Med J 1989;37:28-32)

Drugs may cause thrombocytopenia by three principal mechanisms: suppression of platelet production, direct platelet toxicity, or antibody-mediated platelet destruction (1). With the advent of assays specifically capable of detecting and quantifying IgG on the platelet surface (2), it has become increasingly possible to recognize cases of drug-induced immune thrombocytopenia based on the detection of elevated levels of platelet surface bound IgG in association with ingestion of causative drugs. Consequently, drug-induced immune thrombocytopenia is no longer a disease diagnosed primarily by exclusion. The occurrence of quinidine-induced thrombocytopenia, though uncommon, was documented as early as 1965 (3) and has been thought to be immune in origin (4,5). The platelets themselves may serve as innocent bystanders (6,7) or partial immunogens (8).

We discuss six cases of clinically documented quinidine-induced thrombocytopenia, outlining the mode of diagnosis as well as therapeutic considerations. The ^{125}I-labeled monoclonal anti-IgG assay (2) is used for the quantitation of IgG on the platelet surface. We discuss the role of this assay in diagnosing drug-induced immune thrombocytopenia and address its diagnostic and prognostic value.

Materials and Methods

Patient population

Subjects were retrospectively identified from the data base of the Immune Cytopenia Laboratory. We reviewed the charts of all thrombocytopenic patients seen from 1983 to 1986 whose blood samples had been sent for quantitation of antiplatelet antibodies and who at presentation were noted to be on quinidine. Of a total of 450 samples assayed during that period, 28 index cases were identified and further reviewed.

Selection criteria

To identify cases of quinidine-induced thrombocytopenia, patients had to have a previously known normal platelet count and a documented history of quinidine ingestion. Thrombocytopenia should have developed during quinidine therapy and resolved after discontinuation of the drug (with or without additional therapy). Bone marrow evaluation was required to document adequate marrow megakaryocytes. Patients were excluded if they had any evidence of secondary thrombocytopenia caused by other underlying conditions. Of the 28 index cases, six patients fulfilled the clinical criteria for quinidine-induced thrombocytopenia. The remaining 22 patients were excluded because of the presence of one or a combination of the following exclusion criteria: onset of thrombocytopenia prior to starting quinidine; thrombocytopenia secondary to hypersplenism, septicemia, or disseminated intravascular coagulation (DIC); or primary or chemotherapy-induced marrow hypoplastic state.

Determination of platelet surface bound IgG

Quantitation of IgG on the platelet surface was performed using the radiolabeled monoclonal anti-IgG assay previously described (9). Venous blood was collected in plastic syringes and anticoagulated with acid citrate dextrose A. The whole blood was centrifuged at 200 × g for 20 minutes and the platelet-rich plasma collected. The pH was adjusted to 6.5 with acid citrate dextrose A and then centrifuged at 1,750 × g for 20 minutes. The platelet button was thrice washed in platelet-sus-

Submitted for publication: April 3, 1989.
Accepted for publication: May 23, 1989.

*Formerly Department of Medicine, Henry Ford Hospital. Currently Department of Medicine and Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL.
†Formerly Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL.
‡Immune Cytopenia Laboratory, Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL.
§Department of Medicine and Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL.
Address correspondence to Dr. Saleh, Comprehensive Cancer Center, University of Alabama at Birmingham, LB Wallace Tumor Institute—262, Birmingham, AL 35294.

Table 1
Patient Characteristics

	Patients					
	1	2	3	4	5	6
Age (years)	62	75	72	65	64	58
Sex	M	F	M	F	M	M
Race	W	W	W	W	W	W
Medical history	Ischemic heart disease	Diabetes mellitus, ischemic heart disease, hypertension	Stage D prostatic carcinoma, hypertension, arrhythmias	Ischemic heart disease, arrhythmias	Hypertension, ischemic heart disease	Ischemic heart disease
Duration of quinidine therapy	3 months	2 years	7 days	3 months	5 months	3 years
Additional treatment	Nitroglycerin paste, dipyridamole	Digoxin, insulin	Isosorbide dinitrate, furosemide, digoxin	Nitroglycerin paste, almacone	Digoxin, triamterene	Phenytoin

pension buffer (Dulbecco's phosphate buffered isotonic saline containing 1 g/dL of bovine serum albumin and 4 mmol EDTA, pH 6.5). Ten million washed platelets were incubated with 300 ng ^{125}I-labeled mouse monoclonal anti-IgG in a total volume of 300 μL for 20 minutes at room temperature. Triplicate aliquots of 75 μL (2.5×10^6 platelets) were transferred to Percoll gradient tubes containing 250 μL of isotonic 30% Percoll in saline, centrifuged at 7,500 × g for five minutes, and the tube tip containing the platelet button was transected with a hemostat and razor blade into gamma counting tubes. The number of ^{125}I monoclonal antibody molecules bound per platelet was calculated based on the Avogadro number and the antibody's specific activity and molecular weight (9).

Results

The six patients who fulfilled the selection criteria represented clear-cut cases of quinidine-induced thrombocytopenia. All patients (four males and two females, ranging in age from 58 to 75 years) suffered from ischemic heart disease associated with various arrhythmias and took quinidine in dosages ranging from 200 mg three times daily to 648 mg every six hours (Table 1). The duration of drug ingestion prior to presentation was highly variable, ranging from seven days to as long as three years. The majority of patients, however, had been on quinidine for less than six months. In addition to quinidine, most of the patients were on other medications (Table 1).

Clinical parameters at presentation are given in Table 2. All but one patient were symptomatic. Symptoms consisted primarily of petechia and easy bruisibility. One patient was asymptomatic at presentation despite a platelet count of 6,000/μL. All six patients had a platelet count of less than 55,000/μL, and four had a platelet count less than 10,000/μL at presentation. The severity of thrombocytopenia did not correlate with symptoms at presentation, and none of the patients pre-

Table 2
Clinical Parameters at Presentation

	Patients					
	1	2	3	4	5	6
Chief complaints	Petechiae, bruisibility	Asymptomatic	Bruisibility, epistasis, gum bleed	Petechiae, gum bleed, epistasis	Gum bleed	Bruisibility
Platelet nadir ($\times 10^3/\mu L$)	21	6	3	1	4	49
Antibody level*	3,561	816	1,498	7,610	1,426	1,665
Bone marrow megakaryocytes	Increased	Increased	Increased	Increased	Increased	Increased
Coagulation profile†	Within normal limits	Within normal limits	Within normal limits	Within normal limits	Within normal limits	Within normal limits

*Platelet surface bound IgG (molecules IgG/platelet).
†Prothrombin time; partial thromboplastin time.

Table 3
Clinical Course

	Patients					
	1	2	3	4	5	6
Platelet count at admission ($\times 10^3/\mu L$)	21	6	3	6	4	53
Time point of drug discontinuation	Day 0	Day 0	Day 0	Day 0	Day 0	Day 0
Response to drug discontinuation alone	Yes	Yes	Yes	No	No	No
Additional therapy (day started)	None	None	None	Prednisone (day 4)	Prednisone (day 3)	Prednisone (day 5)
Duration of additional therapy	—	—	—	4 days	7 days then tapered over 8 weeks	3 days
Time point of response (platelet count > 100,000 μL)	Day 5	Day 11	Day 3	Day 8	Day 10	Day 8
Postrecovery platelet counts ($\times 10^3/\mu L$)	233	233	286	209	206	154

sented with or suffered from major bleeding such as gastrointestinal, intracranial, or pulmonary hemorrhage. Peripheral blood smear in all patients revealed greatly decreased circulating platelets, whereas bone marrows consistently showed increased megakaryocytes. Complete coagulation profile was within normal limits in all patients, and no signs of bleeding diathesis were present. Platelet surface bound IgG levels were determined in all patients early on during their hospital course; all patients had elevated values, ranging from 816 molecules IgG/platelet in a patient with a platelet count of 6,000/μL to 7,610 molecules IgG/platelet in a patient with a platelet count of 1,000/μL (normal value < 400 molecules IgG/platelet) (2,10). Platelet surface IgG determination at recovery was performed in only one patient and revealed a value of 400 molecules IgG/platelet.

The disease course of the six patients is summarized in Table 3. Quinidine was discontinued in all patients on the day of admission (day 0) but other medications were continued. Three patients showed a prompt increase in platelet count and complete resolution of thrombocytopenia within three to 11 days (days 3, 5, and 11, respectively) and received no additional treatment. The remaining three patients were started on steroid therapy between days 3 to 5 because of no apparent spontaneous improvement in platelet count up to that time. None of these patients developed bleeding symptoms beyond those noted at presentation. Thrombocytopenia resolved in all three patients within three to four days of steroid initiation, and steroid treatment was discontinued in two of these patients at that time. The remaining patient received full dose prednisone treatment for seven days with subsequent tapering over the next eight weeks. Follow-up platelet counts on all six patients have remained in the normal range. The platelet profile of these patients is shown in the Figure.

The mean recovery time (platelet count > 100,000/μL) for the group was seven days with a range of three to 11 days. Patients who received no additional therapy showed normal platelet counts within a mean of 6.3 days compared to 8.6 days for patients who received steroid therapy.

Discussion

The ^{125}I-labeled monoclonal anti-IgG assay (2) was used to quantitate levels of platelet surface bound IgG in all patients to document the antibody-mediated nature of this disease and to uncover possible prognostic implications of platelet surface bound antibody quantitation.

Differential diagnostic considerations in patients presenting with peripheral thrombocytopenia with adequate marrow megakaryocytes include DIC, posttransfusional purpura, septicemia, thrombotic thrombocytopenic purpura, and immune thrombocytopenic purpura (ITP), both idiopathic and drug-induced. These five categories can be ruled out based on clinical and laboratory findings. Differentiating idiopathic immune thrombocytopenia from secondary drug-induced thrombocytopenia rests primarily on the prompt response and persistent remission of the latter to drug withdrawal with or without a short course of corticosteroids.

Drug-induced thrombocytopenia most commonly occurs in the elderly (11), presumably because of their greater exposure to such drugs. In our patients the duration of quinidine intake was variable, with thrombocytopenia occurring as early as seven days to as late as three years after the start of therapy. These findings indicate that as yet undetermined host-related factors may be responsible for the ultimate pathophysiology of the thrombocytopenic syndrome.

Despite the severity of thrombocytopenia, none of our patients experienced life-threatening bleeding. There was no correlation between symptoms at presentation and severity of thrombocytopenia. This finding is similar to that seen in ITP (12) and contrary to that seen in thrombocytopenia due to myelosuppressive therapy where the incidence of life-threatening bleeding increases significantly as platelet counts fall below 20,000/μL (13). The increased activity of marrow megakaryocytes and the continual production of young, hemostatically active platelets is a possible explanation for the lower incidence of life-threatening hemorrhage in immune platelet destruction syndromes, although the exact reason for platelet hyperfunction in this disease is still undefined.

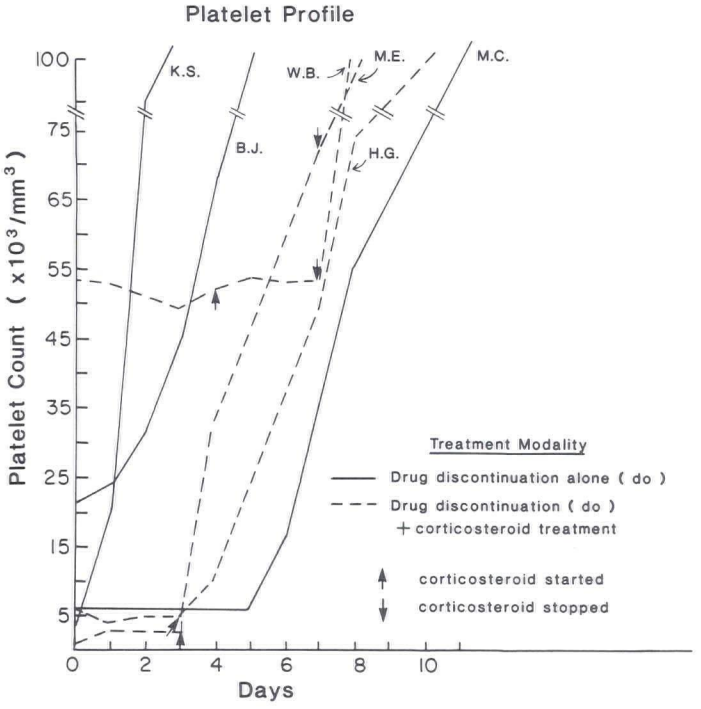
All patients had elevated platelet surface IgG levels, which clearly indicates the role of antibody in this platelet destruction process. The range of platelet surface bound IgG is similar to that described for patients with idiopathic immune thrombocytopenia and is different (higher) than that observed in non-

immune thrombocytopenia (10). The monoclonal anti-IgG assay used in this study differs from assays previously used to quantitate platelet IgG levels in that it measures surface bound IgG rather than total cellular IgG and utilizes a high affinity monoclonal antibody in a direct binding method (2,9,10,14). We found no relationship between the severity of thrombocytopenia and the level of platelet bound IgG in our six patients, which is consistent with findings in ITP and divergent from previously published reports using different assay techniques (10,15). Our finding is not unexpected since a multitude of host-related factors as well as factors related to heterogeneity in terms of subclass content and surface distribution of antibody on the cell surface may determine the ultimate destruction rate of the opsonized target (16,17).

Three of the six patients responded promptly to discontinuation of quinidine with full platelet count recovery within one, three, and five days, respectively. The remaining three patients were started on prednisone therapy, although there was no clinical indication of worsening of any of the symptoms noted at presentation. These patients did not show any spontaneous increment in platelet count three to five days after discontinuing quinidine. Whether the lack of prompt response to drug discontinuation was related to the persistence of circulating drug levels due to delayed clearance/degradation in these patients is unclear. The presence of the offending agent appears to be a prerequisite for the pathogenesis of thrombocytopenia (18). All three patients started on prednisone therapy (1 mg/kg/day) achieved platelet counts of $> 100{,}000/\mu L$ within three to four days. Whether this prompt effect could have been achieved without prednisone therapy is speculative. Prednisone was immediately discontinued in two patients and subsequently tapered over the ensuing eight weeks in the third patient. All three patients maintained normal platelet counts when off steroid therapy. In evaluating the overall clinical course of the patients who received prednisone and those who did not, no difference existed in duration of thrombocytopenia, platelet count at recovery, or symptoms during the hospital course. Initial platelet counts as well as platelet surface bound IgG levels were not significantly different in the two groups.

Use of corticosteroids in the treatment of drug-induced thrombocytopenia remains a clinical judgment call. In the absence of readily available in vitro assays to detect quinidine-dependent antibodies, the following three therapeutic alternatives appear equally acceptable: drug withdrawal accompanied by corticosteroid treatment, drug withdrawal followed by corticosteroid therapy three days later if no reversal of thrombocytopenia is evident, and drug withdrawal with careful observation of platelet count. Patients with drug-induced thrombocytopenia respond promptly to platelet transfusion with adequate hemostasis (19). Thus, patients under observation can be readily managed with platelet support in the event of a potentially life-threatening hemorrhage. In our opinion, most patients can be adequately managed with drug discontinuation and close follow-up without institution of additional therapy.

These six cases of quinidine-induced immune thrombocytopenia were identified based on clinical evidence (quinidine therapy, prompt response to drug cessation with or without corticosteroids, and lack of dependence on corticosteroids for continual remission) in association with elevated platelet surface IgG. Kelton et al (15) have documented the presence of antibody in the serum of such patients which reacts with platelets in a drug-dependent fashion. Obviously, such an assay, if available, is useful for confirming the drug-dependent mechanism. However, such assays are commonly not available or not available in time to be helpful in individual patient care decisions.



Figure—Platelet count profile of study patients.

We feel that new onset of thrombocytopenia in the setting of quinidine administration (particularly if antibody is present on platelet surface) should allow a working diagnosis of drug-induced thrombocytopenia. Treatment should be prompt drug cessation. Depending on clinical evidence, corticosteroids may be added but should be stopped, with subsequent monitoring of platelet count, once the platelet count increases. Persistent normal counts confirm the diagnosis of a drug-dependent syndrome since virtually all patients with idiopathic or secondary immune thrombocytopenia will relapse after seven to ten days of corticosteroid treatment. This approach also limits patient exposure to the serious side effects of corticosteroid therapy.

Acknowledgments

We thank Mrs. Sharon Garrison for her help with manuscript preparation.

This work was supported by grant NIAID 5R01 Al 20792 from the National Institutes of Health.

References

1. Aster RH. Thrombocytopenia due to enhanced platelet destruction. In: Williams WJ, Beutler E, Erslev AJ, Lichtman MA, eds. Hematology. New York: McGraw-Hill Co, 1983:1298.

2. LoBuglio AF, Court WS, Vinocur L, Maglott G, Shaw GM. Immune thrombocytopenic purpura: Use of a ^{125}I-labeled antihuman IgG monoclonal antibody to quantify platelet-bound IgG. N Engl J Med 1983;309:459-63.

3. Vipan WH. Quinidine as a cause of purpura. Lancet 1965;2:37.

4. Moss RA. Drug-induced immune thrombocytopenia. Am J Hematol 1980;9:439-46.

5. Karpatkin S. Drug-induced thrombocytopenia. Am J Med Sci 1971;262:68-78.

6. Miescher PA. Drug-induced thrombocytopenia. Semin Hematol 1973;10:311-25.

7. Shulman NR. A mechanism of cell destruction in individuals sensitized to foreign antigens and its implication in auto-immunity. Ann Intern Med 1965;60:506.

8. Ackroyd JF. The immunologic basis of purpura due to drug sensitivity. Proc R Soc Med 1962;55:30.

9. Court W, LoBuglio A. Measurement of platelet surface bound IgG by a monoclonal ^{125}I-anti-IgG assay. Vox Sang 1986;50:154.

10. Court WS, Bozeman JM, Soong S-j, Saleh MN, Shaw DR, LoBuglio AF. Platelet surface-bound IgG in patients with immune and nonimmune thrombocytopenia. Blood 1987;69:278-83.

11. Bottiger LE, Westerholm B. Thrombocytopenia, II. Drug-induced thrombocytopenia. Acta Med Scand 1972;191:541-8.

12. Karpatkin S. Autoimmune thrombocytopenic purpura. Semin Hematol 1985;22(suppl 4):260-88.

13. Gaydos LA, Freireich EJ, Mantel N. The quantitative relationship between platelet count and hemorrhage in patients with acute leukemia. N Engl J Med 1962;266:905-9.

14. Blumberg N, Masel D, Stoler M. Disparities in estimates of IgG bound to normal platelets. Blood 1986;67:200-2.

15. Kelton JG, Meltzer D, Moore J, et al. Drug-induced thrombocytopenia is associated with increased binding of IgG to platelets both in vivo and in vitro. Blood 1981;58(suppl 3):524-9.

16. Kurlander RJ, Rosse WF, Logue GL. Quantitative influence of antibody and complement coating of red cells on monocyte-mediated cell lysis. J Clin Invest 1977;61:1309-19.

17. Abramson N, Gelfand EW, Jandl JH, Rosen FS. The interaction between human monocytes and red cells: Specificity for IgG subclasses and IgG fragments. J Exp Med 1970;132:1207-15.

18. Christie DJ, Aster RH. Drug-antibody-platelet interaction in quinine- and quinidine-induced thrombocytopenia. J Clin Invest 1982;70:989-98.

19. Moss RA, Castro O. Platelet transfusion for quinidine-induced thrombocytopenia. N Engl J Med 1973;288:522-3.