

THROMBOTIC THROMBOCYTOPENIC PURPURA ASSOCIATED WITH CLOPIDOGREL

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ABSTRACT

Background The antiplatelet drug clopidogrel is a new thienopyridine derivative whose mechanism of action and chemical structure are similar to those of ticlopidine. The estimated incidence of ticlopidine-associated thrombotic thrombocytopenic purpura is 1 per 1600 to 5000 patients treated, whereas no clopidogrel-associated cases were observed among 20,000 closely monitored patients treated in phase 3 clinical trials and cohort studies. Because of the association between ticlopidine use and thrombotic thrombocytopenic purpura and other adverse effects, clopidogrel has largely replaced ticlopidine in clinical practice. More than 3 million patients have received clopidogrel. We report the clinical and laboratory findings in 11 patients in whom thrombotic thrombocytopenic purpura developed during or soon after treatment with clopidogrel.

Methods The 11 patients were identified by active surveillance by the medical directors of blood banks (3 patients), hematologists (6), and the manufacturers of clopidogrel (2).

Results Ten of the 11 patients received clopidogrel for 14 days or less before the onset of thrombotic thrombocytopenic purpura. Although 10 of the 11 patients had a response to plasma exchange, 2 required 20 or more exchanges before clinical improvement occurred, and 2 had relapses while not receiving clopidogrel. One patient died despite undergoing plasma exchange soon after diagnosis.

Conclusions Thrombotic thrombocytopenic purpura can occur after the initiation of clopidogrel therapy, often within the first two weeks of treatment. Physicians should be aware of the possibility of this syndrome when initiating clopidogrel treatment. (*N Engl J Med* 2000;342:1773-7.)

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THROMBOTIC thrombocytopenic purpura is a life-threatening, multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, neurologic changes, and renal abnormalities.¹ Idiopathic cases occur at a rate of 3.7 per year per million persons, and the mortality rate for promptly treated cases ranges from 10 to 20 percent.²⁻⁵ Many drugs have been associated with the syndrome.⁶ In cases that have been investigated, its cause appears to be related to autoantibodies against a metalloprotease that degrades

von Willebrand factor.⁷⁻⁹ Impaired proteolysis of von Willebrand factor leads to the binding of unusually large multimers to platelets and results in the platelet microthrombi that characterize the syndrome. The presence of IgG autoantibodies against the protease distinguishes thrombotic thrombocytopenic purpura from related syndromes, including the hemolytic-uremic syndrome.^{7,8}

Ticlopidine, an antiplatelet drug, has been associated with the development of thrombotic thrombocytopenic purpura, with an estimated incidence of 1 case per 1600 to 5000 patients treated.¹⁰⁻¹³ Clopidogrel is a new antiplatelet drug that has achieved widespread clinical acceptance because it has a more favorable safety profile than ticlopidine.¹⁴ The two drugs are structurally related derivatives of thienopyridine, differing only by one carboxymethyl group. They have short half-lives in the circulation and different metabolites.¹⁵ The drugs act by blocking an adenosine diphosphate-binding site on platelets, which inhibits the expression of the glycoprotein IIb/IIIa receptor in the high-affinity configuration that binds fibrinogen and large multimers of von Willebrand factor. Because phase 3 clinical trials and studies involving 20,000 closely monitored patients who were treated with clopidogrel have not reported neutropenia, adverse skin or gastrointestinal effects, or throm-

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botic thrombocytopenic purpura — all of which have been associated with ticlopidine therapy — clopidogrel has largely replaced ticlopidine in clinical practice for the prevention of stroke and thrombosis in patients who have received coronary-artery stents and in patients with peripheral vascular disease or acute cardiac ischemia.^{16,17}

For all new drugs, a comprehensive assessment of safety requires diligent post-marketing surveillance. Ticlopidine-associated thrombotic thrombocytopenic purpura was not widely recognized until seven years after the drug was approved by the Food and Drug Administration (FDA), despite its use by several million patients.¹⁰⁻¹³ Since clopidogrel was approved by the FDA in early 1998, more than 3 million people have received the drug, and two cases of thrombotic thrombocytopenic purpura that occurred after clopidogrel use have been reported at medical conferences.^{18,19} In the current study, we determined the clinical characteristics, the interval between clopidogrel treatment and the onset of disease, the response to treatment, outcomes, and laboratory findings in 11 patients in whom thrombotic thrombocytopenic purpura developed during or soon after treatment with clopidogrel.

METHODS

Eleven cases of thrombotic thrombocytopenic purpura among patients who were treated with clopidogrel were identified between March 1998 and March 2000 by active surveillance by the medical directors of blood banks (three patients), hematologists (six), and a surveillance program overseen by Sanofi-Synthelabo and Bristol-Myers Squibb, the manufacturers of clopidogrel (two). Two of these patients have been described previously.^{18,19} To be included in the study, a patient had to have previously taken or still be taking clopidogrel when he or she received a diagnosis of thrombotic thrombocytopenic purpura on the basis of clinical and laboratory findings. For most patients, the results of additional laboratory studies were not available that could be used to distinguish thrombotic thrombocytopenic purpura from other disorders that may be associated with thrombocytopenia and microangiopathic hemolysis.^{7,8}

RESULTS

The 11 patients ranged in age from 35 to 70 years (median, 55) (Table 1). Six patients were women. Six patients had received clopidogrel for coronary artery disease, including three patients who received the drug after the placement of a coronary-artery stent. Concomitant medications included the cholesterol-lowering drugs atorvastatin and simvastatin in five patients, two of whom had begun taking the drug within the three weeks before the onset of thrombotic thrombocytopenic purpura; long-term treatment with atenolol in three patients; and long-term cyclosporine treatment in one patient who had undergone kidney-pancreas transplantation. Clopidogrel had been used for 3 to 14 days in all but one patient (Patient 10). Patient 4 had discontinued clopidogrel 3 weeks before the onset of the syndrome, and thrombotic thrombocytopenic purpura had oc-

curred after 21 days of atorvastatin therapy. The other 10 patients stopped taking clopidogrel when thrombotic thrombocytopenic purpura began. Only Patient 2 had received ticlopidine previously, two years before the onset of the syndrome, and no thrombocytopenia or hemolysis had occurred during the earlier treatment.

Thrombotic thrombocytopenic purpura was manifested by thrombocytopenia and microangiopathic hemolytic anemia, with or without neurologic changes or renal dysfunction (Table 1). Platelet counts were less than 20,000 per cubic millimeter in 10 patients, and hematocrit values were less than 27 percent in 8 patients. Seven patients had neurologic changes, including disorientation (in two patients), slurred speech (in two), confusion (in one), aphasia (in one), and coma (in one). Four patients had renal insufficiency, characterized by a serum creatinine level of more than 2.5 mg per deciliter (221 μ mol per liter), including one who was undergoing long-term dialysis after an unsuccessful renal transplantation and one who was receiving long-term cyclosporine treatment. This last patient, who had undergone kidney-pancreas transplantation five years earlier, had normal renal function, but the onset of the syndrome was manifested by an acute decrease in renal function, thrombocytopenia, and microangiopathic hemolysis. A renal biopsy, performed because of concern over the possibility of kidney rejection in association with the rising serum creatinine level, revealed platelet microthrombi. Two patients had evidence of acute liver injury, with marked elevation of serum aminotransferase levels.

All patients underwent plasma exchange, with resolution of symptoms and laboratory abnormalities occurring after a median of 8 plasma exchanges (range, 1 to 30) in 10 patients. Patient 9 died after four days of plasma exchange. Patient 1 had a recurrence immediately after undergoing coronary-artery bypass surgery, 73 days after the diagnosis of thrombotic thrombocytopenic purpura. He had a second recurrence 2 months later, after receiving atorvastatin for 14 days. Each recurrence responded quickly to plasma exchange.¹⁹ Patient 10 had three recurrences, the last occurring seven months after the discontinuation of clopidogrel; each recurrence responded to plasma exchange. None of the 10 surviving patients were rechallenged with clopidogrel.

Plasma samples from Patients 1 and 2 were available for the measurement of von Willebrand factor-cleaving protease activity and the inhibitory activity of IgG, according to previously published techniques.⁷ In both patients, during episodes of thrombotic thrombocytopenic purpura, von Willebrand factor-cleaving protease activity was undetectable and IgG inhibitors of the protease were present. Concentrations of 3.2 mg of IgG per milliliter in the case of Patient 1 and of 2.5 mg of IgG per milliliter in the case of Patient 2

TABLE 1. CLINICAL CHARACTERISTICS AND TREATMENT OF 11 PATIENTS WITH THROMBOTIC THROMBOCYTOPENIC PURPURA AFTER CLOPIDOGREL THERAPY.

CHARACTERISTIC	PATIENT 1*	PATIENT 2†	PATIENT 3	PATIENT 4	PATIENT 5	PATIENT 6	PATIENT 7	PATIENT 8‡	PATIENT 9	PATIENT 10	PATIENT 11
Age (yr)	55	54	66	61	36	49	49	35	60	65	70
Sex	M	M	F	M	F	F	F	M	F	M	F
Duration of clopidogrel therapy (days)	7	14	14	3	10	8	8	3	5	330	7
Platelet count <20,000/mm ³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Hematocrit <27 percent	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serum creatinine >2.5 mg/dl (221 μmol/liter)	No	No	Yes§	No	No	No	Yes	Yes	Yes	No	No
Neurologic changes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
Rose and Eldor score¶	3	3	6	2	5	5	7	5	6	6	5
Schistocytes on peripheral-blood smear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serum lactate dehydrogenase (U/liter)	2500	933	1765	2349	1239	1100	1645	929	4118	791	235
No. of plasma exchanges	12	30	20	6	6	13	7	4	NA	10	1

*Patient 1 has been described previously.¹⁹

†Patient 2 has been described previously.¹⁸

‡Patient 8 had normal renal function and a one-month history of failing pancreatic function five years after undergoing kidney-pancreas transplantation. The patient had been receiving cyclosporine for the five years before the onset of thrombotic thrombocytopenic purpura.

§Patient 3 had undergone unsuccessful renal transplantation and was undergoing dialysis before the onset of thrombotic thrombocytopenic purpura.

¶The severity of disease was assessed with the Rose and Eldor scoring system, which evaluates the platelet count, the hemoglobin level, the serum creatinine level, and neurologic function.²⁰ Each category is given a score of 0 (normal findings), 1 (mildly abnormal clinical or laboratory findings), or 2 (markedly abnormal clinical or laboratory findings) on the basis of specific criteria; a total combined score of 4 or more indicates a diagnosis of severe thrombotic thrombocytopenic purpura. A platelet count of more than 100,000 per cubic millimeter is assigned a score of 0, a count of 20,000 to 100,000 per cubic millimeter a score of 1, and a count of less than 20,000 per cubic millimeter a score of 2. A hematocrit value of more than 36 percent is assigned a score of 0, a value of 27 to 36 percent a score of 1, and a value of less than 27 percent a score of 2. A serum creatinine level of less than 1.5 mg per deciliter (133 μmol per liter) is assigned a score of 0, a level of 1.5 to 2.5 mg per deciliter a score of 1, and a level of more than 2.5 mg per deciliter a score of 2. A score of 0 is assigned if no neurologic deficits are present; a score of 1 if confusion, lethargy, or behavioral changes are present; and a score of 2 if a focal deficit, convulsions, stupor, or coma is present.

||NA denotes not available. Patient 9 died after four days of plasma exchange.

were required to inhibit protease activity by 50 percent in mixtures containing 12 percent plasma from a normal subject. During remission three months after plasma exchange, the protease activity in plasma samples from Patient 2 was 67 percent of the mean (±SD) value (103±12 percent) in plasma samples from 57 normal subjects, and at a concentration of 6.6 mg per milliliter, his IgG caused no inhibition of the protease activity in the mixing assay.

DISCUSSION

We reviewed the clinical and laboratory findings in 11 patients in whom thrombotic thrombocytopenic purpura developed during or soon after treatment with clopidogrel. Thrombotic thrombocytopenic purpura can result in multiorgan dysfunction or death. In our patients, the disease was characterized by the occurrence of thrombocytopenia, microangiopathic hemolytic anemia, neurologic changes, and renal dysfunction during treatment with clopidogrel or, in one patient, soon after treatment was stopped. One pa-

tient died, eight had complete resolution of thrombotic thrombocytopenic purpura after the discontinuation of clopidogrel and treatment with plasma exchange, and two had relapses up to seven months after the onset of the syndrome, with rapid recovery after plasma exchange.

The features of thrombotic thrombocytopenic purpura in patients who received ticlopidine and in those who received clopidogrel can be contrasted, despite marked differences in the methods used to ascertain cases. First, unlike the cases reported among ticlopidine-treated patients, 95 percent of which occurred after 2 to 12 weeks of treatment, all but one of the cases among clopidogrel-treated patients occurred within 2 weeks after the initiation of treatment.^{10-12,21,22}

Second, whereas in almost all patients with ticlopidine-associated thrombotic thrombocytopenic purpura who had a response to plasma exchange, the response occurred after 7 or fewer plasma exchanges and there were no relapses,¹³ two patients in our study required 20 or more plasma exchanges before the

symptoms and laboratory abnormalities resolved, and two patients had a total of five relapses.

Third, only 57 percent of the previously reported cases of ticlopidine-associated thrombotic thrombocytopenic purpura were treated with plasma exchange,¹³ as compared with all the cases in our study. Rather than attributing the clinical symptoms to coronary procedures or vascular disease, physicians' heightened awareness of the possibility of thrombotic thrombocytopenic purpura may have led to early diagnosis and use of plasma exchange in our patients. Among patients who were treated with plasma exchange, 18 percent of those with ticlopidine-associated thrombotic thrombocytopenic purpura died (11 patients), as compared with 9 percent of our patients with clopidogrel-associated disease (1 patient). Fifty-eight percent of the patients (22) with ticlopidine-associated thrombotic thrombocytopenic purpura who did not undergo plasma exchange died.^{10,13} We have previously reported that the overall mortality rate for ticlopidine-associated cases was 33 percent, in part due to lower rates of use of plasma exchange, particularly in patients older than 60 years of age.^{10,13}

Finally, the use of cholesterol-lowering drugs was not evaluated in the patients with ticlopidine-associated cases; almost half the patients with clopidogrel-associated cases had received cholesterol-lowering drugs. In one of our patients, thrombotic thrombocytopenic purpura appeared to be induced by atorvastatin, and one patient had a recurrence during treatment with atorvastatin that responded quickly to plasma exchange.¹⁹ One case of thrombotic thrombocytopenic purpura has been reported after short-term treatment with simvastatin.²³ The possibility that cholesterol-lowering drugs and clopidogrel may have adverse pharmacologic interactions in some patients deserves further study.

The mechanism by which clopidogrel could cause thrombotic thrombocytopenic purpura is not known. Patients with idiopathic^{7,8} and ticlopidine-associated²⁴ thrombotic thrombocytopenic purpura have an immune-mediated deficiency of von Willebrand factor–cleaving protease activity in plasma — a finding that distinguishes this syndrome from the clinically related hemolytic–uremic syndrome. Laboratory studies in two of our patients revealed that during the acute phase of the disease, IgG inhibitors of the protease were detectable and the plasma was severely deficient in protease activity. During clinical remission in one patient, plasma protease activity had increased to a nearly normal level and the patient's IgG did not inhibit protease activity. However, it is premature to conclude on the basis of these findings that clopidogrel causes an immune reaction to the protease. The number of cases that have been investigated is small, and a limited number of plasma samples from affected patients are available. Furthermore, in some patients the syndrome occurred after

three or five days of clopidogrel treatment, which makes an antibody-mediated mechanism induced by clopidogrel seem unlikely. These observations suggest that despite having similar chemical structures, clopidogrel and ticlopidine may cause thrombotic thrombocytopenic purpura by different mechanisms. Unlike ticlopidine, clopidogrel has not been associated with apoptosis of microvascular endothelial cells in culture.²⁵

Our findings have important clinical implications. Clopidogrel has largely replaced ticlopidine in clinical practice.^{15,16} One of the reasons for this change was the association of ticlopidine use with thrombotic thrombocytopenic purpura. Other reasons were the lower rates of skin, hematologic, and gastrointestinal adverse effects associated with clopidogrel and its more convenient dosing schedule.¹⁴ Our cases of thrombotic thrombocytopenic purpura after treatment with clopidogrel appear to differ from cases associated with the use of ticlopidine in that they occurred soon after the initiation of therapy, were prone to recurrence, and required up to 30 plasma exchanges before clinical improvement occurred. The development of cardiac or neurologic changes after the initiation of clopidogrel therapy may be mistakenly attributed to the underlying condition for which it was prescribed. Physicians should be aware of the possibility of thrombotic thrombocytopenic purpura among patients who are receiving clopidogrel.

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