Thrombotic Thrombocytopenic Purpura Associated With Ticlopidine in the Setting of Coronary Artery Stents and Stroke Prevention

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Background: One of the most unusual causes of thrombotic thrombocytopenic purpura (TTP), a life-threatening disease, is ticlopidine hydrochloride, an antiplatelet agent used to prevent strokes in high-risk populations or following coronary artery stent placement. Recently, Hoffman-LaRoche Pharmaceuticals, following reports of 20 deaths from ticlopidine-associated TTP, updated the information about the hematologic adverse effects of the drug.

Objectives: To review our recent findings on ticlopidine-associated hematologic toxic effects, which served as the impetus for the revised warnings, and to discuss the implications of these findings.

Methods: Data were obtained from the Food and Drug Administration’s MedWatch program, published phase 3 clinical trials and case reports, hematologists, and plasmapheresis centers.

Results: No cases of TTP have been reported in phase 3 ticlopidine trials. In contrast, postmarketing surveillance has identified serious adverse drug reactions to ticlopidine, resulting in 259 deaths, with TTP accounting for 40 of these deaths. Detailed information was available on 98 cases of ticlopidine-associated TTP. Compared with 42 patients in the coronary artery stent setting, 56 patients with ticlopidine-associated TTP in the stroke prevention setting were more likely to be women (62.5% vs 28.6%; \( P = .01 \)). Before the onset of TTP in patients receiving stroke prevention therapy and patients with stent placement, ticlopidine had been used for less than 2 weeks in 5.4% and 2.4%, between 2 and 3 weeks in 17.9% and 21.4%, between 3 and 4 weeks in 30.4% and 38.1%, and between 4 and 12 weeks in 46.4% and 38.1%, respectively. Death occurred in almost 60% of all patients not receiving plasmapheresis compared with 21.9% of patients receiving plasmapheresis for stroke prevention and 14.3% of patients receiving plasmapheresis in the stent setting.

Conclusions: Use of ticlopidine requires frequent physician visits and laboratory tests for at least 3 months in the stroke prevention setting, while, with short-term use in the coronary artery stent setting, adverse events are less likely to occur. These factors, as well as competition from clopidogrel bisulfate, a new antiplatelet agent, potentially limit the feasibility of ticlopidine as a stroke prevention agent, while having less impact on its use following coronary artery stent placement.

Arch Intern Med. 1999;159:2524-2528

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening, multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic changes, renal failure, and fever. The cause of acute TTP appears to be related to transient immune dysregulation and selective antigenic targeting of a metalloprotease that degrades large multimers of factor VIIIIR.\(^2\)\(^3\) Ultralarge factor VIIIIR multimers increase platelet adhesiveness in vitro and may be one of the platelet-aggregating agents responsible for the platelet microthrombi that characterize TTP in vivo.\(^4\) An IgG autoantibody against components of the enzyme may account for a lack of metalloprotease activity in patients with TTP. While the reasons for transient immune dysregulation and for the selective antigenic targeting of the protease are unknown, the time course of 2 to 4 weeks following certain drug exposures is consistent with an autoimmune mechanism for some cases of TTP.

One example of a drug-associated cause of TTP is ticlopidine hydrochloride, an antiplatelet agent that in 1997 was used by 1 million individuals in the United States for stroke prevention and, more recently, by more than 600,000 individuals following coronary artery stent placement.\(^5\)\(^6\) The estimated incidence of ticlopidine-associated TTP is 1 in 1600, while its mortality rate is 33%.\(^5\)\(^7\) Herein, we re-
view our recent findings about ticlopidine-associated hematologic toxic effects, including TTP; postulate on the potential mechanism of ticlopidine-associated TTP; and outline the implications of our findings for patients and physicians involved in clinical trials or clinical practice with ticlopidine as a stroke prevention agent or following coronary artery stent placement.

### RESULTS

In phase 3 clinical trials in the stroke prevention setting, significant differences in the rates of neutropenia in the ticlopidine vs aspirin groups were observed in the 2 large stroke prevention studies, the Canadian American Ticlopidine Study (1.0% vs 0.2%) and the Ticlopidine Aspirin Stroke Study (0.9% vs 0.0%). In contrast, STARS and ISAR, the 2 largest phase 3 clinical trials of antiplatelet agents in the setting of coronary artery stents, found no difference in rates of neutropenia in the ticlopidine groups and the control groups (0.5% vs 0.0% in ISAR and 0.2% vs 0.0% in STARS) during the 1-month observation period. No cases of TTP were reported in these phase 3 trials.

Data from the FDA’s MedWatch program indicated that the most common serious ticlopidine-associated toxic effects were hematologic, reported in 1756 cases, primarily leukopenia, thrombocytopenia, TTP, agranulocytosis, pancytopenia, and aplastic anemia. Overall, 259 of the cases resulted in death, with 85.6% of these deaths being associated with hematologic toxic effects of the drug. Despite being infrequently reported, thrombocytopenia (50 deaths) and TTP (40 deaths) were more common causes of death than leukopenia (34 deaths) and agranulocytosis (22 deaths).

In contrast to the absence of reports of ticlopidine-associated TTP cases in the phase 3 clinical trial setting, we identified 56 cases of ticlopidine-associated TTP in the stroke prevention setting and 42 cases of ticlopidine-associated TTP following coronary artery stent placement. The mean age of the patients undergoing stroke prevention was 66.9 years (SD, 11.8 years); for the patients with stent placement, 62.4 years (SD, 11.5 years) (P<.05). Normal platelet counts within 2 weeks of the onset of TTP were documented in most patients in both groups. Before the onset of TTP in patients undergoing stroke prevention and stent placement, ticlopidine had been used for less than 2 weeks in 5.4% and 2.4%, between 2 and 3 weeks in 17.9% and 21.4%, between 3 and 4 weeks in 30.4% and 38.1%, and between 4 and 12 weeks in 46.4% and 38.1%, respectively. Manifestations of TTP in the stroke prevention and coronary artery stent setting were similar, including thrombocytopenia (69.6% vs 76.2% had platelet counts < 20 × 10^9/L); anemia (hemoglobin levels were <0.09 g/L in 26.8% and 26.2%); and neurologic changes, including focal deficits, convulsions, and/or coma (in 75.0% vs 69.1%). Renal insufficiency with a serum creatinine level greater than 221 μmol/L (>2.5 mg/dL) was more common in the stroke prevention vs coronary artery stent setting (35.7% vs 19.1%) (P<.05 for all comparisons). Overall TTP mortality in the stroke prevention setting was 37.5% vs 28.6% in the coronary artery setting (P>.05). Plasmapheresis was performed in 57.1% of the patients undergoing stroke prevention and in 66.7% of the patients with stent placement. When both groups of patients were combined to determine overall mortality rates associated with plasmapheresis, the mortality rate for all patients who did not undergo plasmapheresis was 57.9%, while the mortality rate for all patients who underwent plasmapheresis was 18.3% (P<.001).

### COMMENT

While ticlopidine is approved by the FDA for the prevention of thrombotic strokes in aspirin-intolerant high-
risk individuals, off-label use includes primary stroke prevention therapy in aspirin-tolerant individuals. In 1998, more than 2 million persons received ticlopidine (IMS America, Philadelphia, Pa, oral communication, October 30, 1998). Clinical trials have identified neutropenia as the most common serious adverse effect of ticlopidine use in the stroke prevention setting, with an incidence of 1.0% to 2.4% in most clinical trials.⁵,¹³ As a consequence, in 1991, the pharmaceutical manufacturer of the drug, concerned about patient safety, provided warnings to physicians and included a “black box” section in the original package insert describing the potential for neutropenia and encouraging physicians to closely monitor complete blood cell counts every 2 weeks for 3 months.¹⁵

Dangerous adverse effects of drugs are commonly discovered after marketing, with more than half of FDA-approved drugs having serious adverse effects that were not detected in clinical trials.¹⁶ Such was the case with ticlopidine. After initial marketing, reports of an additional serious adverse effect began to surface, with 25 TTP cases being identified in the MedWatch database.¹⁷ In 1994, the package insert was amended to include a bold-faced typed statement that TTP can occur in rare circumstances. However, underrecognition of ticlopidine-associated TTP continued, as noted in 1998 publications⁵,⁷ of 60 cases and 20 deaths from ticlopidine-associated TTP, raising additional questions about the safety of ticlopidine. The pharmaceutical manufacturer again revised the ticlopidine package insert in 1998 to include a black box warning section with statements describing an estimated incidence of ticlopidine-associated TTP of 1 in 2000 to 1 in 4000 individuals, the need for extreme vigilance for TTP, the signs and symptoms of TTP, and the importance of early diagnosis and treatment.⁵ Furthermore, concern over whether inclusion of TTP in the black box revision would be overlooked by physicians led the pharmaceutical manufacturer to send a “Dear Doctor” letter describing the revisions to all neurologists and cardiologists in the United States.

Our results have practical implications for clinical practitioners. Since hematologic adverse effects almost always occur within the first 3 months of ticlopidine therapy, patients who receive longer-term ticlopidine therapy will need weekly or biweekly physician visits to monitor complete blood cell counts. Patients who are ticlopidine intolerant or who react to aspirin should be evaluated with laboratory tests, including complete blood cell count and creatinine level determination, should be checked for neutropenia, thrombocytopenia, anemia, or renal insufficiency. An abnormally low hematocrit or platelet count should be followed with a peripheral smear review looking for schistocytes. Cases with a high index of suspicion should be treated emergently with plasmapheresis, which can reduce the expected chances of death by 67%. As noted in several of the case reports, progression of symptoms can occur within hours. The most important factor associated with survival was receipt of plasmapheresis. Patients with ticlopidine-associated TTP is fatal in more than 60% of patients who discontinue ticlopidine use but do not undergo timely therapeutic plasmapheresis. Physician evaluation should include specific attention to skin rashes, which may predate the onset of TTP in some individuals or represent purpura in others, or neurologic changes, which can be easily confused with stroke symptoms and lead to a delay in diagnosis and subsequent initiation of plasmapheresis. The results of laboratory tests, including complete blood cell count and creatinine level determination, should be checked for neutropenia, thrombocytopenia, anemia, or renal insufficiency. An abnormally low hematocrit or platelet count should be followed with a peripheral smear review looking for schistocytes. Cases with a high index of suspicion should be treated emergently with plasmapheresis, which can reduce the expected chances of death by 67%. As noted in several of the case reports, progression of symptoms can occur within hours. The most important factor associated with survival was receipt of plasmapheresis. Patients with ticlopidine-associated TTP in the setting of stroke prevention were less likely to undergo plasmapheresis, a factor that may account for the trend toward a higher mortality rate in this setting.

Our findings do not imply that ticlopidine should no longer be used following coronary artery stent place-
ment. Clinical trials have shown that ticlopidine is of added benefit when combined with aspirin. The first randomized trial (ISAR) found that, at 30 days of follow-up, the ticlopidine group had 75% fewer cardiac end points than the phenprocoumon group (1.6% vs 6.2%; \( P < .001 \)) and had 0% vs 5.0% episodes of stent thrombosis. The largest study (STARS) found that combined antiplatelet therapy with ticlopidine and aspirin had an 80% reduction at 30 days in the combined end point of death, Q-wave myocardial infarction, emergency surgery, target vessel revascularization, and angiographic thrombosis (0.5%) compared with aspirin plus warfarin (2.7%; \( P = .007 \)) or aspirin alone (3.6%; \( P < .001 \)). Hall and co-workers found a 1-month stent thrombosis rate of 2.9% in an aspirin-only group and 0.8% in a ticlopidine-aspirin group, although the results did not reach statistical significance because of a small sample size. Taken together, a recommendation shortening ticlopidine therapy from 4 to 2 weeks seems most prudent and is consistent with patterns of care in many centers in the United States. Most cases of stent thrombosis in the warfarin stenting era occurred within 2 weeks of stent placement. In STARS, stent thrombosis occurred at a mean of 0.7 days. Almost 90% of the cases of TTP following a coronary artery stent procedure have occurred more than 2 weeks after ticlopidine initiation. Also, a preliminary report from the Mayo Clinic (Rochester, Minn) has documented no increase in adverse events with coronary stenting when ticlopidine use was shortened from 4 to 2 weeks.

Concerns over hematologic complications may have broad implications for antiplatelet agents. In 1998, the FDA approved an alternative antiplatelet agent, clopidogrel bisulfate, a thienopyridine derivative that differs structurally from ticlopidine by the addition of a carboxymethyl side group, as a potentially less toxic alternative to ticlopidine. Developed because clopidogrel did not show bone marrow toxicity in tissue culture and animal models, the large study of clopidogrel vs aspirin in patients at risk for ischemic events found the incidence of severe neutropenia with clopidogrel about the same as for aspirin (0.1% vs 0.2%), and no cases of clopidogrel-associated TTP were reported. Its antithrombotic activity is similar to that of ticlopidine, requiring its conversion to an active metabolite by the hepatic cytochrome P-450-1A. Clopidogrel-induced agranulocytosis was reported during the trial of clopidogrel vs aspirin in patients at risk for ischemic events (CAPRIE). While many physicians have switched from prescribing ticlopidine to prescribing clopidogrel, vigilance for hematologic complications, including agranulocytosis and TTP, with this new agent is advised. It took 6 years for widespread recognition of ticlopidine-associated TTP to occur. If similar rates of clopidogrel-associated TTP adverse effects occur (ie, 1 in 1600 patients), several years may elapse before similar numbers of cases associated with clopidogrel are identified in the literature.

In 1997, ticlopidine was used by more than 2 million individuals as primary stroke prevention therapy and following coronary artery stent placement. In 1998, awareness of ADRs to ticlopidine had increased, yet as many as 1250 cases and 400 deaths from ticlopidine-associated TTP were expected to occur, if prompt recognition and treatment was not undertaken. In practice in the stroke prevention setting, vigilance for ticlopidine-associated hematologic toxic effects will undoubtedly lead to an increase in the number of physician visits and complete blood cell count tests ordered in the first 3 months of ticlopidine therapy or a switch to alternative antiplatelet agents such as clopidogrel. In contrast, in the coronary artery stent setting, ticlopidine plus aspirin is highly effective in minimizing the risk of stent thrombosis and major cardiac complications. With closely monitored use of 2 to 4 weeks of ticlopidine therapy following coronary artery stent placement, serious hematologic complications from ticlopidine should be avoidable. Taken together, the 1998 black box revision in the package insert, the Dear Doctor letter from the pharmaceutical manufacturer, and competition from clopidogrel will almost certainly adversely affect the future use of ticlopidine.

Accepted for publication March 15, 1999.

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The opinions expressed in this article are solely those of the authors and do not represent opinions of the Food and Drug Administration, the Department of Veterans Administration, or Northwestern University, Chicago, Ill.

Presented in part at the Food and Drug Administration Meeting, Rockville, Md, March 1998; the American Society of Hematology Meeting, San Diego, Calif, December 1997; and the American College of Cardiology Conference, Dallas, Tex, November 1998.

We thank Steven Fredd, MD, Ray Lipich, MD, and Diane Wysowski, PhD, for their comments and input before our presentation at the Food and Drug Administration; Attila Kursun, MD, John Godwin, MD, David Green, MD, PhD, and Hau Kwaan, MD, PhD, for comments on this and related articles; and the patients with thrombotic thrombocytopenic purpura whose comments and committed interest in this project were responsible for the continuation of these study efforts for the past 2 years.

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REFERENCES


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