Clopidogrel-associated Severe Isolated Thrombocytopenia — A Case Report

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Clopidogrel is a new oral antiplatelet agent with structure and mechanism of action similar to ticlopidine. It has replaced ticlopidine for many years due to significantly lower side effects and simpler dosing regimen. Cases of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) associated with clopidogrel were reported in recent years, but only 1 case of isolated profound thrombocytopenia associated with clopidogrel was ever reported. We present our experience with a case of severe isolated thrombocytopenia without evidence of TTP and HUS after clopidogrel administration. No drug possibly associated with thrombocytopenia was prescribed concomitantly. Platelet count recovered rapidly after discontinuation of clopidogrel and 8 units of platelet transfusion.

Key Words: Clopidogrel • Thrombocytopenia • Purpura

INTRODUCTION

Clopidogrel, a thienopyridine derivative, irreversibly inhibits ADP-induced platelet aggregation by inhibiting binding of ADP to its receptor and subsequent ADP-mediated activation of glycoprotein IIb/IIIa complex. Clopidogrel was approved by the United States (U.S.) Food and Drug Administration (FDA) in November 1997 and has been used in more than 3 million patients worldwide. It has been approved in the U.S. for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction or established peripheral vascular disease.

There were many reports concerning the potentially fatal types of hematologic dyscrasias associated with ticlopidine therapy, such as agranulocytosis, aplastic anemia, neutropenia, pancytopenia, thrombocytopenia and thrombotic thrombocytopenic purpura (TTP). We experienced a fatal case that had severe isolated thrombocytopenia induced by ticlopidine in a very short time. Clopidogrel has a lower frequency of associated TTP than ticlopidine, a lower rate of neutropenia, and better gastrointestinal tolerance. Because of its better side-effect profile and similar dosing regimen, clopidogrel has largely replaced ticlopidine. The excellent safety and tolerability profile of clopidogrel compares favorably with that of aspirin as documented in the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study. In fact, in the CAPRIE study, clopidogrel was more effective than aspirin in reducing atherosclerotic events in high-risk patients. The overall tolerability associated with the use of clopidogrel appears to be similar to that of aspirin; however, gastrointestinal bleeding may occur less often with clopidogrel.

In recent years, several cases of TTP and hemolytic uremic syndrome (HUS) associated with clopidogrel were reported. Only 1 case of isolated profound thrombocytopenia associated with clopidogrel has ever been reported; in that case, platelet count recovered after intravenous immunoglobulin (IVIG) administration.
We report a case of clopidogrel-associated severe isolated thrombocytopenia with rapid recovery of platelet count upon discontinuation of clopidogrel and 8 units of platelet transfusion.

CASE REPORT

The patient, a 72 y/o man, had history of hypertensive cardiovascular disease (HCVD), chronic atrial fibrillation and peptic ulcers. He had no previous history of thrombocytopenia and had never taken ticlopidine or aspirin before. Two-dimensional echocardiogram and single photon emission computed tomography (SPECT) thallium stress scan revealed myocardial ischemia and damage in the anterobasal wall of the left ventricle. No coronary angiography was done. The patient was given antithrombotic medication for primary prevention of cerebrovascular and major vascular accidents due to multiple risk factors, including old age, HCVD, chronic atrial fibrillation, and possible concomitant coronary artery disease. Clopidogrel (75 mg/day) was used in place of aspirin or warfarin due to history of active peptic ulcer since July 1, 2002. The patient had normal baseline platelet count of 248 × 10^9/L on July 2, 2002.

Forty-seven days later, this patient suffered from dyspnea, tarry stool and red-colored urine. Physical examination revealed crackles at the left lower zone of the lung field, and purpura and ecchymosis in both forearms. Chest radiography revealed left side pleural effusion. We performed diagnostic thoracocentesis and hemothorax was detected. In addition, hematuria and upper gasterointestinal (UGI) tract bleeding were confirmed by urine analysis and positive stool occult blood test. Severe isolated thrombocytopenia (1 × 10^9/L) was found and was also confirmed by a repeated platelet count and peripheral blood smear examination. The patient’s body temperature was within normal limits. His consciousness was clear, and no neurologic abnormality was noted. Mild prerenal azotemia (BUN: 42 mg/dl, Cr: 1.8 mg/dl on August 17, 2002) relating to UGI tract bleeding was also observed. The condition was improved obviously after adequate fluid supplement and blood transfusion (BUN: 22 mg/dl, Cr: 1.3 mg/dl on August 19, 2002). Neither schistocytes nor other abnormalities suggesting a microangiopathic hemolysis were noted by peripheral blood smear (Figure 1). We also performed bone marrow study, and no abnormality was detected. Serum lactate dehydrogenase (LDH) level was elevated (894 IU/L) which was thought to be related to liver damage, while abdominal sonography revealed parenchymal liver disease and gall bladder stones plus elevation of liver enzymes (alanine aminotransferase: 70 IU/L, aspartate aminotransferase: 86 IU/L). The patient’s fibrinogen level was normal. Clopidogrel was therefore discontinued immediately and 8 units of platelets were given. Platelet counts at 36 and 60 hours following platelet transfusion were increased to 37 × 10^9/L and 70 × 10^9/L (Figure 2), respectively. Hemothorax and hematuria improved significantly, and no additional blood transfusion was needed. Platelet count recovered to 207 × 10^9/L on August 22, 2002 (about 100 hours following the discontinuation of clopidogrel) and the patient was discharged.

DISCUSSION

The most common causes of severe thrombocytopenia are medications, TTP-HUS and disseminated intravascular coagulation (DIC). TTP-HUS is an inclusive term describing diverse syndromes of multiple etiologies with common features of thrombocytopenia and microangiopathic hemolytic anemia. Other organ involvement, including renal failure, neurologic abnormalities, and gastrointestinal symptoms, are common. In DIC, there is not only severe thrombocytopenia but also obvious low fibrinogen level.
Our patient had a normal baseline platelet count before clopidogrel treatment. We could exclude TTP-HUS by both peripheral blood smear without evidence of microangiopathic hemolytic anemia and no evidence of major organ involvement. DIC was excluded by normal fibrinogen level. He did not receive any medication other than clopidogrel which was likely to induce severe thrombocytopenia (e.g., heparin, abciximab). After discontinuing administration of clopidogrel, the platelet count recovered spontaneously. Clopidogrel-associated severe isolated thrombocytopenia was thus diagnosed.

Clopidogrel-associated TTP-HUS had been reported frequently in recent years. Bennett et al. reported 11 patients who developed TTP during or soon after treatment with clopidogrel. TTP can occur after the initiation of clopidogrel therapy, often within the first 2 weeks of treatment. All 11 patients had thrombocytopenia and microangiopathic hemolysis, and most showed neurologic changes or increase in serum creatinine levels. A report from FDA revealed TTP-HUS happened in 1.54% of the patients receiving clopidogrel treatment. Thrombocytopenia, DIC, platelet disorders, idiopathic thrombocytopenic purpura and coagulation disorder were also reported to be associated with clopidogrel administration. The exact mechanism of hematologic dyscrasia associated with clopidogrel is still unclear. Isolated profound thrombocytopenia associated with clopidogrel has only been reported once. That patient received heparin and clopidogrel treatment due to acute coronary syndrome and the platelet count declined to $3 \times 10^9$/L from $180 \times 10^9$/L during a period of 1 week. After stopping clopidogrel and prescribing IV IgG, the platelet count recovered to $241 \times 10^9$/L in about 200 hours. Heparin-induced thrombocytopenia was considered, and the treatment of IV IgG might be controversial. In addition, 2 cases related to clopidogrel-associated thrombocytopenia have been reported, but severities of thrombocytopenia in those cases were minor (platelet counts: $70 \times 10^9$/L and $22 \times 10^9$/L, respectively). Our patient didn’t receive heparin before thrombocytopenia appeared and was treated only with 8 units of platelet transfusion. Platelet counts recovered faster than previously reported. This experience identified that clopidogrel can induce severe and reversible isolated thrombocytopenia, and no specific treatment was needed in this condition in addition to immediately discontinuing the drug.

CONCLUSION

This report raises the concern of a potential adverse drug reaction. Although the exact mechanism is unclear, it
is highly likely that clopidogrel causes severe hematologic dyscrasia such as severe isolated thrombocytopenia in rare cases. Physicians should be aware of the possibility of this rare and reversible adverse effect when initiating clopidogrel treatment.

REFERENCES

藥物 (Clopidogrel) 引起之嚴重性單獨血小板過低

— 病例報告

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Clopidogrel 是近三年來常使用的新上市抗血小板藥物，由於安全性已受到廣泛認可而被普遍使用且幾乎完全取代 Ticlopidine，其腸胃道副作用亦明顯少於 Aspirin；雖然安全，但近年仍不乏該藥物所造成的血液病變，例如 TTP (thrombotic thrombocytopenic purpura) 及 HUS (hemolytic uremic syndrome)，但目前僅有一病例報告造成嚴重性單獨血小板減少症。我們報告一位患者在服用 Clopidogrel 一個月後，出現嚴重性單獨血小板減少情形，期間並未使用其他可能導致血小板減少之藥物，亦無任何臨床證據顯示為 TTP、HUS 或 DIC。除了入院當天輸血小板八個單位之外，我們並未給予病患其他相關的治療，血小板數目於停藥後 100 個小時內迅速而顯著的上昇，並回到正常範圍。

關鍵詞：Clopidogrel、血小板減少症、紫斑。