University Heart Journal
Vol. 5, No. 2, July 2009

CASE REPORTS

Clopidogrel Induced Haematological Dyscrasia: A Case Report

Abdul Wadud Chowdhury[1], Amanullah Bin Siddiq[1],
A.E.M. Mazharul Islam[1], Amitav Saha[1].

[1]Department of Cardiology, Dhaka Medical College Hospital, Dhaka.

Address for Communication
Dr. Abdul Wadud Chowdhury. Associate Professor,
Department of Cardiology, Dhaka Medical College, Dhaka.
E-mail: drwadud@hotmail.com

Abstract

Clopidogrel is an analogue of ticlopidine, used for reduction of atherosclerotic events in patients with acute coronary syndrome (ACS), stroke, peripheral arterial disease and for elective percutaneous coronary intervention (PCI). It selectively and irreversibly blocks ADP binding to platelets. Its primary side effect is bleeding. However potentially fatal types of haematological dyscrasia such as aplastic anaemia, neutropenia, thrombocytopenia, pancytopenia may be associated with clopidogrel therapy. A 50 years old diabetic, hypertensive lady with angina was started to treat with clopidogrel along with other anti-ischaemic and anti-hypertensive drugs. Subsequently the patient developed leucopenia and thrombocytopenia after starting of clopidogrel. Five days later her complete blood count returned to normal after withdrawal of both anti platelets. Aspirin was re-introduced with great precaution. Later repeat leucocyte and platelet count were found to be normal. At follow-up 1 month after discharge patient found asymptomatic with normal blood count. To the best of our knowledge, clopidogrel induced haematological dyscrasia was not reported earlier in our country.

Key words : Acute coronary syndrome, percutaneous coronary intervention.

Introduction

Clopidogrel is a thienopyridine derivative, indicated for the reduction of atherosclerotic events in patients with acute coronary syndrome (ACS), stroke, peripheral arterial disease[1]. It is also used in elective PCI, coronary artery bypass grafting (CABG) and aspirin resistant case[2,3]. It inhibits platelet aggregation, increases bleeding time and reduces blood viscosity by inhibiting ADP action on platelet receptor[4]. It has fewer side effects than ticlodipine or aspirin[5]. However, there were several reports concerning the potentiality of fatal types of haematological dyscrasia associated with clopidogrel therapy such as aplastic anaemia, neutropenia, pancytopenia, thrombocytopenia and thrombocytopenic purpura (TTP)[6-10]. Here we are reporting a rare side effect of clopidogrel- leucopenia and thrombocytopenia in a patient with unstable angina.

Case Report

A 50 years old hypertensive lady was on medication-angiotensin converting enzyme inhibitor (ACE inhibitor) and aspirin for 15 years under regular supervision of her family physician. Recently she developed new onset diabetes mellitus (DM) and stable angina with fluctuation of blood pressure for last three weeks. DM was well controlled by diet and exercise. So her physician added two new drugs- clopidogrel and nitrate with her previous medication. Seventeen days later suddenly she developed severe compressive chest pain with nausea, sweating and admitted into a private hospital. Both general and systemic examination findings were normal. Her ECG showed non-specific T-wave changes and cardiac troponin-I was negative. Echocardiography showed normal left ventricular function (ejection fraction 75%) without any wall motion abnormality. She was diagnosed as a case of unstable angina and treated conservatively. But her complete blood count (CBC) with peripheral blood film (PBF) showed leucopenia (1000/cmm) and thrombocytopenia (110000/cmm) with normal differential count, Hb%- 13gm/dl, ESR- 30mm in 1st hour. Fasting blood sugar was 7.75mmol/dl and fasting lipid profile showed dyslipidaemia. Blood urea, serum creatinine, Chest x-ray P/A view, USG of whole abdomen, urine R/M/E, blood culture showed normal finding. Surprisingly she had no features of bleeding manifestation and secondary infection. On enquiry, she had no history of recent sore throat, fever, cough, urinary or bowel complaints, arthritis. She was not having any antibiotics. Both clopidogrel and aspirin were discontinued. Broad-spectrum antibiotics were started immediately. Five days after discontinuation of anti platelets, CBC showed- leucocyte and platelet count returned to their normal range (8500/cmm & 200000/cmm respectively). Aspirin was re-introduced with great precaution. Five days later, repeat CBC with PBF was found to be normal. The patient was discharged without any complication. At follow-up after one month and three month from discharge, her CBC and

platelet count were found quite normal. Patient also remained asymptomatic.

Discussion

Clopidogrel is indicated for secondary prevention of atherothrombotic events. It is used singly or combination with aspirin for the treatment of ACS. Ticlodipine, first widely used thienopyridine derivative has been studied extensively. Its use declined after recognition of haematological side effects- neutropenia 2%-3%, agranulocytosis, and thrombotic thrombocytopenic purpura. So the use of clopidogrel is increasing day by day. The most commonly reported adverse event of clopidogrel is bleeding. Very rare cases of blood dyscrasia including agranulocytosis, neutropenia, thrombocytopenia, aplastic anaemia or pancytopenia were also observed in some case reports[7-10]. Among these haematological abnormalities, neutropenia associated with clopidogrel appears to be very rare. The risk of neutropenia is less than ticlodipine and essentially equivalent to aspirin. In CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, severe neutropenia was observed in six patients. Among them four were on clopidogrel and two were on aspirin therapy. Two of 9,599 patients who received clopidogrel and none of 9,586 patients who received aspirin had neutrophil count of zero[5]. In CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial, the number of patients with thrombocytopenia (19 Clopidogrel & aspirin versus 24 aspirin & placebo) or neutropenia (3 versus 3) were similar[11]. The mechanisms of leucopenia and thrombocytopenia are not clearly understood. But the mechanism of action of clopidogrel is believed to be identical to that of ticlodipine. The drugs are similar in structure and have similar effects - both desired and adverse[12]. The risk of myelotoxicity with clopidogrel is considerable when fever or other sign of infection without any apparent cause is present. Two case reports of neutropenia associated with clopidogrel in chronic renal failure were documented after 20-45 days administration of clopidogrel and took recovery time of 5days[7,12]. In our patient bicytopenia was found as an incidental finding after 17 days of clopidogrel therapy in a patient with normal renal function and took recovery time of 5 days.

An evaluation was taken to find out other possible causes of bicytopenia. On this regard, she had no history of fever, cough, arthritis, rash, bowel or urinary complaints. She was not having any antibiotics. Both general and systemic examination findings revealed no abnormality. This virtually excluded the other viral, infectious and systemic causes of bicytopenia. All reported cases as well as our case showed spontaneous recovery of leucocyte and platelet count to their normal range after 5 days withdrawal of clopidogrel. Here aspirin was readminstered after recovery and did not affect the CBC.

The temporal relation between development of bicytopenia after initiation of clopidogrel and rapid recovery after withdrawal of drug testifies in favour of drug induced reversible haematological dyscrasia.

Conclusion

The exact mechanism and incidence of clopidogrel induced haematological dyscrasia is unknown yet. Clopidogrel can produce primary bleeding complication as well as some rare haematological dyscrasia specially neutropenia. So it is important for physician to remember that clopidogrel can produce some rare life-threatening haematological side effects both in patient with normal renal function and impaired renal function.

References

1. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effcts of ticlodipine and clopidogrel. Ann Intern Med 1998;129:394-05.
2. Lionel HO, Bernard JG. Drugs for the heart. 6th Edition
3. Kastrati A, et al. A clinical trail of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. N Eng J Med 2004;350:232-38.
4. Storey RF, May JA, Heptinstall S: Potentiation of platelet aggregation by heparin in human whole blood is attenuated by P2Y12 and P2Y1 antagonists but not aspirin. Thromb Res 2005 115:301-7.
5. CAPRIE steering committee. A randomized, blind trial of clopidogrel versus aspirin in patients at risk of ischemic events. Lancet1996; 348:1329-39.
6. Mayer B, StaudingerT, Leehner K. Clopidogrel and aplastic anemia. Lancet 2001; 357:1446-47.
7. Akcay A, Kanbay M, Agca E, Sezer S, Oezer S, Ozdemir FN. Neutropenia due to clopidogrel in a patient with end stage renal disease. Ann Pharcother 2004(Sep); 38(9): 1538-49.
8. Andres E, Altanne EPM, Bemald G, Schlienger JL. Febrile pancytopenia associated with clopidogrel. Arch Intern Med 2001;161-125.
9. Elmi F, Peacock T, Schiavone J. Isolated profound throbocytopenia associated with clopidogrel. J Invasive Cardiol 2000; 12:36-38
10. Dominique S, Kenneth B, Kassler TB, et al. Clopidogrel and throbocytopenic purpura. N Eng J Med 2000; 343:1191-94.
11. Mitka M. Results of CURE trial for acute coronary syndrome. JAMA.2001; 285:1828-29.
12. Doogue MP, Begg EJ, Bridgman P. Clopidogrel Hypersensitivity Syndrome with Rash, Fever, and Neutropenia.Mayo Clin Proc October2005; 80(10):1368-70.