Symbiosis

www.symbiosisonline.org
www.symbiosisonlinepublishing.com

Case Report | Journal of Emergency, Critical Care and Diagnostic Management | Open Access

Massive Hematuria in Relation to the Use of Ticagrelor: Case Report

Halil Cebeci, Halil Dogan

Department of Emergency Medicine, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

Received: August 20, 2018; Accepted: September 26, 2018; Published: September 27, 2018

***Corresponding author:** Halil Dogan, Department of Emergency Medicine, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey, Email: drhalildogan@gmail.com*

Abstract

Major clinical benefits of antiplatelet therapy initiated after acute coronary syndrome (ACS) have been demonstrated in cardiovascular clinical trials and Dual antiplatelet therapy consisting of a P2Y12 receptor antagonist with aspirin is recommended as part of standard therapy for secondary protection. However, bleeding episodes that develop during antiplatelet therapy are significant problems. Ticagrelor is a newly developed reversible P2Y12 antagonist antiplatelet agent. This agent, which is part of standard antiplatelet therapy with aspirin, also causes additional bleeding risk. In this case; we present a case of massive hematuria which is a rare side effect due to use of ticagrelor which is used for a treatment after a non-ST-elevated myocardial infarction (NSTEMI) with a percutaneous coronary intervention.

Keywords: Dual Antiplatelet Therapy; Hematuria; Hemorrhage; Ticagrelor;

Introduction

Platelets bind to the subendothelial matrix (adhesion) after endothelial damage due to atherosclerotic plaque rupture and form clot formation as aggregate with other platelets. With the understanding of this central function of platelets in cardiovascular thrombosis, dual antiplatelet therapy composed of an antiplatelet agent and aspirin is become a significant component of standard treatment in ACS. One of the newly developed oral antiplatelet agents, ticagrelor, has been found to be more advantageous than clopidogrel because of its rapid onset of action, reversible platelet inhibition and providing for a stronger platelet inhibition without varying from patient to patient in complete platelet inhibition [1]. In a randomized, double-blind, placebo-controlled Phase III trial PLATO (Platelet Inhibition and Patient Outcomes), the rate of total bleeding complications with Ticagrelor was 16.1% and the rate of major bleeding was 11.6%. Fatal bleeding was reported at 0.3%. Spontaneous urinary tract bleeding was observed in 58 of 9235 patients (0.6%) in the group using ticagrelor. No fatal case was reported from patients with urinary system hemorrhage [2]. Other common side effects frequently seen with ticagrelor are dyspnea, bradycardia, pulmonary congestion, and ventricular pause [3].

In this case; we present a case of massive hematuria which is a rare side effect due to use of ticagrelor which is used for a treatment after a non-ST-elevated myocardial infarction (NSTEMI) with a percutaneous coronary intervention.

Case Report

A 73-year-old male patient was admitted to the emergency departments with complaints of blood in his urine. The patient was diagnosed with NSTEMI 10 days ago and coronary angiography was performed, and a stent was applied in the right coronary artery (RCA). For 10 days, he used 180 mg/day of ticagrelor and 100 mg/day of acetyl salicylic acid. He has been diagnosed before with chronic obstructive pulmonary disease, essential hypertension and coronary artery disease.

On physical examination the patient was generally in good condition, conscious, orientated, and cooperative; blood pressure was 175/67 mm/Hg, pulse rate was 93/minute, body temperature was 36.5 °C, and oxygen saturation was 87%. He has no lateralized neurological deficit, the cranial nerve and cerebellar examinations were natural, muscle strength was at 5/5 level on four limbs and no sensory abnormality was detected. Both lungs participated equally in respiration in the respiratory system examination. There have been rales in the middle and lower zones of the bilateral lungs, and respiratory sounds were roughly heard. There was no costovertebral angle sensitivity and no tenderness on the abdomen. Gross hematuria was present. On cardiovascular system examination, s1 and s2 heart sounds were heard naturally and rhythmically, no additional sound and murmur were heard. The patient does not have jugular venous distention but has bilateral ++ pretibial edema.

In the first examination, hemoglobin (Hgb) was 13.4 g/dl (normal is 12.9-15.9 g/dl); leucocyte was 15.8 10^3/ul (normal is 3.7-10.1 10^3/ul); c-reactive protein was 10.94 mg/dl (normal is <0.5 mg/dl); troponin T was 0.201 ng/ml (normal is <0.1 ng/ml); lactate was 2.92 mmol/L (normal is 0.5 - 2.0 mmol/L); urea was 62 mg/dl (normal is 16.6-48.5 mg/dl); creatine was 1.75 mg/dl (normal is 0.7-1.2 mg/dl); prothrombin time was 15.2 sec. (normal is 10.4-14.5 sec.); the international normalized ratio was 1.24 (normal is 0.8-1.2). The urine density in the urine sample was 1009, the pH of the urine was 5. In the urine microscopy,

610 erythrocytes and 152 leucocytes were counted in each magnification area. The urinary ultrasonography was evaluated as normal. The Hgb amounts in the control bloodwork were measured as 11.96 g/dl, 12.66 g/dl, 12.54 g/dl, and 11.49 g/dl, respectively.

The patient has no significant decrease in the Hgb values, troponin values fell. Hematuria was observed with urinary catheter and urine color was clarified in 24 hours. The patient was consulted with Urology and Cardiology departments and discharged with the recommendation of the Urological policlinic control examination.

Discussion

Despite the clinical benefits of treatment with clopidogrel, this antiplatelet agent possesses some drawbacks, such as having a slow onset of action, making irreversible P2Y12 inhibition, and having variable pharmacokinetic and pharmacodynamic outcome profiles. Ticagrelor is a reversible and selective inhibitor of P2Y12 receptors and a drug from the first-generation *cyclopentyl-triazolo-pyrimidine* class. It is rapidly absorbed following oral intake and has 7 to 12 hours half-life. Unlike thienopyridines, which must be metabolized in the liver via the cytochrome p450 system and which is a prodrug and must be converted to active metabolites, ticagrelor is directly active after oral administration. In contrast to thienopyridines, ticagrelor is a reversible inhibitor of P2Y12 receptors. Ticagrelor, as compared with thienopyridines, is more advantageous because of its rapid onset of action (approximately 2 hours), making more consistent and stronger platelet inhibition, it does not require hepatic metabolism to be active. Reversible effects of ticagrelor (ticagrelor half-life 7-12 hours, clopidogrel 11 days, prasugrel 2-4 days) brings it to the forefront for early loading in patients whose coronary anatomy is unknown in ACS and in patients to whom coronary artery bypass graft may need to be administered [4].

Despite the clinical benefits on prevention of stent thrombosis and re-infarction after ACS, antiplatelet therapy is associated with increased risk of bleeding. In the PLATO study, the risk of total bleeding with ticagrelor was higher than with clopidogrel, with no significant difference in major and life-threatening bleeding rates [5].

Despite reduced cardiovascular mortality and morbidity with antiplatelet therapy, we are confronted with an increased risk of bleeding. In the PLATO trial, the ratio of major and minor total bleeding was found to be 16.1% with ticagrelor (14.6% with clopidogrel). In the same study, the rate of major bleeding with ticagrelor was 11.6% (11.2% with clopidogrel). Fatal course bleedings were reported at 0.3% for both drugs [2]. In the study, non-procedural spontaneous urinary tract bleedings were seen in 58 cases of 9235 patients using ticagrelor [2], 13 of which were major bleedings and 4 were life-threatening bleedings [6] (54 cases of 9186 patients using clopidogrel had urinary system bleeding [2], 14 of which were major bleedings and 4 were life-threatening bleedings [6]). There were no fatal cases in patients with urinary system hemorrhage in both groups [6]. Due to hemorrhagic complications, 2.4% of patients using ticagrelor had to discontinue medication (1% with clopidogrel). The rate of patients who were discontinued due to hematuria was 0.1% for both drugs [2]. Higher age, decreased creatinine clearance, lower Hgb ratio and female sex were associated with increased risk of major bleeding [2].

There is not yet enough study about which antiplatelet agent should be used in patients who develop bleeding complication in the literature review and when the medicine should be discontinued. At the same time, case reports regarding bleeding complications related to the use of ticagrelor are limited. In a study by Subiakto and colleagues, 100 patients who were prescribed ticagrelor were prospectively followed up, 5 patients developed bleeding (three with gastrointestinal bleeding, two with subcutaneous bruising), and clopidogrel was started instead of ticagrelor [3]. In one case, which spontaneous omental hemorrhage was observed, aspirin and ticagrelor were not given to the patient 24 hours. The day after the operation, aspirin treatment was initiated at a daily dose of 100 mg, and treatment with clopidogrel at the dose of 75 mg / day was continued without loading [7]. In another case of spontaneous subdural hematoma, the patient was admitted to the hospital for conservative treatment and follow-up. Ticagrelor was discontinued for antiplatelet therapy and continued with aspirin and clopidogrel [8].

There is no direct inhibitor of oral antiplatelet agents and treatment options are limited in cases of bleeding. In a study conducted by Hansson et al., platelet aggregability was ex-vivo tested and compared by adding platelets to the blood samples of the patient group using aspirin and ticagrelor and compared with the patient group using aspirin and clopidogrel. Results have been reported by stimulating separately platelet aggregation with arachidonic acid (AA), thrombin receptor activator peptide-6 (TRAP) and adenosine diphosphate (ADP). While all three activators showed an increase in platelet aggregation, the aggregation induced by ADP was significantly lower than the others [9]. In a study by Nylander and colleagues on mice, the amount of ticagrelor-induced bleeding was reduced by 65% with Factor VIIa, and the prolonged bleeding time was shortened by 72%. In the same study, a 63% decrease in the amount of bleeding and a 93% shortening at the bleeding time were reported in the group tested with Factor VII. But this has not been confirmed on people [10].

In a dual antiplatelet treatment guide published by with the collaboration of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) in 2017, the use of scoring systems to assess the risk of post-PCI thrombosis and bleeding has been found clinically impractical. At the same time, platelet function testing or genetic studies are not recommended in the setting of dual antiplatelet therapy except in special cases (e.g. patients with recurrent adverse events) [11].

Transition to prasugrel or ticagrelor to clopidogrel in patients with minor bleeding or in patients with a high risk of major bleeding is a common practice. However, there are no strong randomized data showing long-term efficacy and safety of drug replacement [11].

A switching algorithm among antiplatelet agents has been proposed by observing pharmacodynamic studies, because of the widespread use in clinical practice and the necessity of switching between medications for reason drug intolerance or side effects. According to the recommended algorithm for follow-up of patients with complications of bleeding in the guide, it is recommended to continue dual antiplatelet therapy for spontaneous hemorrhage, which does not require medical intervention and further examination. It has recommended continuation of dual antiplatelet therapy and shortening the duration of treatment or switching to another less potent agent (e.g. prasugrel/ticagrelor to clopidogrel) in patients with mild bleeding (blood loss <3 g / dL Hgb) and followed by unattended follow-up to the hospital. In moderate-severe bleeding that followed by hospitalization or the blood loss is > 3 g / dL Hgb, it recommends terminating the dual antiplatelet therapy and consider transitioning to single antiplatelet treatment or shortening the period of treatment or switching to a less potent agent. Patients with hemodynamically stable severe hemorrhage (blood loss > 5 g / dL Hmg) requiring hospital admission are advised to terminate treatment if the bleeding cannot be controlled with the same recommendations. It is recommended that treatment be terminated promptly in patients with life-threatening hemorrhage (massive genitourinary, gastrointestinal or respiratory bleeding, active intracranial, spinal or intraocular hemorrhage, hemodynamic unstable patients). It has been emphasized that once the moderate, serious and life-threatening hemorrhage has been controlled, the patient must be reassessed for the continuity of single or double antiplatelet therapy without loss of time [11]. But the level of evidence for these proposals is low.

In this case with massive hematuria, we did not have a significant drop in hemoglobin. The patient was hemodynamically stable and did not require transfusion. The urine color returned to normal. The benefit of antiplatelet therapy with ticagrelor considered as more efficient so it was decided that the patient's treatment should be continued. The patient was discharged with suggestion of early-stage outpatient clinic control from the urology and cardiology departments.

Conclusion

Dual antiplatelet therapy, which has become a standard treatment regimen for the prevention of recurrent cardiovascular events has also brought increased risk of bleeding. Ticagrelor has a higher rate of bleeding, although it is more effective than clopidogrel in preventing cardiovascular events and reducing deaths due to ACS. There is not yet enough data on the circumstances in which patients who have bleeding complications will benefit from termination of treatment. Treatment options for bleeding patients are limited due to the lack of a specific inhibitor of antiplatelet agents. Patients on antiplatelet therapy need further research that focuses on the management of bleeding complications.

Acknowledgement

Informed Consent: The patient has given consent for this case report to be published.

References

1. Michelson AD. Antiplatelet therapies for the treatment of cardiovascular disease. Nat Rev Drug Discov. 2010;9(2):154-169. doi: 10.1038/nrd2957
2. Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, et al. Bleeding complications with the P2Y12receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient outcomes (PLATO) trial. Eur Heart J. 2011;32(23):2933-2944. doi: 10.1093/eurheartj/ehr422
3. Subiakto I, Asrar ul Haq M, Van Gaal WJ. Bleeding risk and incidence in real world percutaneous coronary intervention patients with ticagrelor. Heart Lung Circ. 2015;24(4):404-406. doi: 10.1016/j.hlc.2014.10.006
4. Capodanno D, Dharmashankar K, Angiolillo DJ. Mechanism of action and clinical development of ticagrelor, a novel platelet ADP P2Y12 receptor antagonist. Expert Rev Cardiovasc Ther. 2010;8(2):151-158. doi: 10.1586/erc.09.172
5. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet. 2010;375(9711):283-293. doi: 10.1016/S0140-6736(09)62191-7
6. Dinicolantonio JJ, D'Ascenzo F, Tomek A, Chatterjee S, Niazi AK, Biondi-Zoccai G. Clopidogrel is safer than ticagrelor in regard to bleeds: A closer look at the PLATO trial. Int J Cardiol. 2013;168(3):1739-1744. doi: 10.1016/j.ijcard.2013.06.135
7. Cheng VE, Oppermen A, Natarajan D, Haikerwal D, Pereira J. Spontaneous Omental Bleeding in the Setting of Dual Anti-platelet Therapy with Ticagrelor. Heart Lung Circ. 2014;23(4):e115-7. doi: 10.1016/j.hlc.2013.11.002
8. Suryanarayana Sharma PM, Tekkatte Jagannatha A, Javali M, Hegde AV, Mahale R, Madhusudhan, et al. Spontaneous subdural hematoma and antiplatelet therapy: Does efficacy of Ticagrelor come with added risk?. Indian Heart J. 2015;67 Suppl 3:S30-5. doi: 10.1016/j.ihj.2015.06.024
9. Hansson EC, Shams Hakimi C, Åström-Olsson K, Hesse C, Wallén H, Dellborg M, et al. Effects of ex vivo platelet supplementation on platelet aggregability in blood samples from patients treated with acetylsalicylic acid, clopidogrel, or ticagrelor. Br J Anaesth. 2014;112(3):570-575. doi: 10.1093/bja/aet339
10. Nylander S, Pehrsson S, Hansson K. Ticagrelor-Induced Bleeding in Mice Can Be Reversed By Fviia (Novoseven®) and Fii. J Am Coll Cardiol. 2013;61(10):E212. doi:10.1016/S0735-1097(13)60213-2
11. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease Developed in Collaboration with EACTS. Eur Heart J. 2018;39(3):213-260. doi: 10.1093/eurheartj/ehx419