CASE REPORT

Prasugrel-related hepatotoxicity

Zeki Dogan, Mustafa Yurtdas, Gokhan Bektasoglu

Abstract

Prasugrel is usually preferred over Clopidogrel to reduce the risk of recurrent coronary thrombosis in patients who undergo percutaneous coronary interventions during an acute coronary syndrome owing to its more potent and more rapid antithrombotic activation. Little is known about Prasugrel-induced hepatotoxicity, although mild-to-moderate alanine transaminase (ALT) and gamma glutamyl transpeptidase (GGT) elevations have been noticed in post-marketing surveillance. Herein, we report the case of a patient with Prasugrel-related hepatotoxicity that was reverted after switching from Prasugrel to Ticagrelor.

Keywords: Percutanous coronary interventions, antiplatelet drug, Prasugrel, hepatotoxicity.

DOI: https://doi.org/10.47391/JPMA.3179

Introduction

Thrombocytes have an important role in the occurrence of stent thrombosis, which is the major cause of ischaemic coronary events in the early stage after percutaneous coronary intervention (PCI). Therefore, antithrombotic therapy is the mainstay of treatment to prevent ischaemic coronary events in patients undergoing PCI. Prasugrel is a new oral antithrombotic thienopyridine agent that irreversibly blocks adenosine diphosphate (ADP) receptors (P2Y12) on thrombocytes.[1,2] Prasugrel is usually preferred over Clopidogrel to reduce the risk of recurrent coronary thromboses in patients who undergo PCI during an acute coronary syndrome owing to its more potent and more rapid antithrombotic activation.[3] As well as its beneficial effects, it has several side effects such as mostly bleeding (usually epistaxis), and rarely headache, fatigue, nausea, arthralgias, rash, and hypersensitivity reactions. Little is known about Prasugrel-induced hepatotoxicity, although mild-to-moderate ALT and GGT elevations in post-marketing surveillance is noticed. Here, we report the case of a patient with a probable Prasugrel-related hepatotoxicity that was reverted after switching from Prasugrel to Ticagrelor.

Department of Cardiology, Istanbul Atlas University, School of Medicine, Medicine Hospital, Turkiye.

Correspondence: Zeki Dogan. e-mail: drzeki@yahoo.com

Case

A 63-year-old male patient with poorly controlled diabetes for 20 years was admitted to the emergency department of Istanbul Atlas University School of Medicine Hospital, Istanbul, Turkiye in November 2019 due to pressure-like chest pain radiating to the left arm lasting for two days. Also, he was being treated with Acetylsalicylic acid, Clopidogrel, Metoprolol, and Ramipril because of the stent placed in the left anterior descending artery (LAD), for the last four months. Electrocardiography showed inverted T wave in V1-V6 precordial leads. Echocardiography revealed akinesis of the left ventricular anterior wall and apex, with an ejection fraction of 40%. In laboratory analysis, slightly elevated troponin level and normal hepatic function tests were observed. Laboratory findings are shown in Table. The patient's history revealed that the statin treatment had been stopped in the second month after the patient's first PCI procedure because of generalised muscle pain and arthralgia, hence the patient was not on any statin for the last three months. He denied alcohol consumption or herbal medications. His physical examination was within normal limits. There was no clubbing, rash, hepatosplenomegaly or any sign of acute or chronic hepatic/cholecystic disease. Finally, the patient was diagnosed with non-ST-elevation myocardial infarction (NSTEMI). Coronary angiography showed a thrombotic

Table: Laboratory findings of the patient.

	Admission	After Prasugrel use	Discharge
Creatinine	1.02 (0.7-1.2 mg/dl)	1.71 (2.51)	1.04
BUN	19 (8.4-25.7 mg/dl)	27.7/ max 56.7	22.9
Glucose	275		
AST	22 (5-34 U/L)	676/ max 1270	42
ALT	23 (< 55 U/L)	969/ max 1357	64
GGT	105	361/ max 420	98
ALP	97 (40-130 U/L)	255/ max 280	143
LDH	102 (125-243 U/L)	298/ max 353	220
Total Bilirubin	0.9 (0.2-1.25 mg/dl)	11.66/ max 12.78	6.0
Direct Bilirubin		8.16/ max	5.36
HbA1c	9.0 (%)	-	7.7
Amoniac	(31-123 mcg/dl)	60	
Amylase	-	(U/L)	107
Lipase	-	(U/L)	70
INR	0.94 (0.8-1.2)	1.93/ max 2.49	1.37
CRP	2.6	75/max 137.7	27.52
Hb	10.7 (g/dl)	9.6	10.1

* Laboratory values measured at third day (maximum values); BUN: Blood Urea Nitrogen, INR: International Normalized Ratio, CRP: C-Reactive Protein, Hb: Haemoglobin.

stenosis of 95% in stent on mid-LAD. Because of thrombotic nature of the lesion, Clopidogrel was discontinued and Prasugrel was started (60mg orally once as loading dose, then 10mg/day orally in combination with aspirin 100mg/day). Then, a predilatation was performed with a 3.0x20mm sized balloon catheter followed by an implantation of 3.5x24 mm sized drug-eluting stent without any complications, and full patency was obtained with a maximum contrast dose of 60ml. On the second day of hospitalisation, since an increase in creatinine value was discovered (the first creatinine value was 0.88 and the second day it was 1.71 mg dL), it was decided to retain the patient in hospital with guideline-based treatment and volume replacement. On the third day of hospitalisation, general weakness and mild abdominal pain were observed. On the fourth day, the patient had a tendency to sleep, his sclera was observed to be icteric, and his urine was dark. There was pain and tenderness in the right upper quadrant of the abdomen. Initially, aspartate transaminase (AST) was 22 UI/L, alanine transaminase (ALT) 23 UI/L, gamma glutamyl transpeptidase (GGT) 105 UI/L, lactat dehydrogenase (LDH) 102 U/L, alkaline phosphatase (ALP) 97 UI/L, total bilirubin (TB) 0.9 mg/dL, and INR 0.94 (Table).

Creatinine value was 1.0 mg/dL. Abdominal ultrasonography and computed tomography (CT) scan revealed normal liver and biliary tract findings along with normal dimensions of hepatic vein and inferior vena cava. Cranial imaging studies were within normal limits. The patient's body temperature was 37.7°C (did not rise above this level). CRP was 22 mg/dL, procalcitonin was normal. Serologic tests for hepatitis A, B, C, and E, and Epstein-Barr virus and cytomegalovirus were negative. Also, tests for autoimmune diseases (such as liver kidney microsomal antibodies, anti-nuclear antibody, anti-mitochondrial antibody and anti-smooth muscle antibody) were negative. Since only Prasugrel had been added to the medicines that the patient had been using for a long time before admission, it was thought that the current clinical picture could be related to the use of Prasugrel. For that reason, on the fifth day, Prasugrel was stopped, and Ticagrelor was started instead (a loading dose of oral 180mg followed by 90mg twice daily). Three days after the drug change, AST increased to 1270 U/L, ALT to 1357 U/L, bilirubin to 12.78mg/dL (predominantly direct bilirubin), and INR to 2.49. Fever and CRP started to return to normal level. Fourteen days after the change in drug, the patient's clinical status improved with normalisation of liver and biliary tract function tests. The patient was discharged with long-term medical therapy including Ticagrelor, Acetylsalicylic acid, Metoprolol, Statin, and Ramipril. After three months of follow-up, the patient had an asymptomatic clinical status with normal hepatobiliary biochemistries.

Discussion

Antithrombotic therapy is a cornerstone in the treatment of patients undergoing PCI, regardless of the underlying clinical picture. Novel antithrombotic drugs have a crucial role in the management of stent thrombosis. Prasugrel is a new Thienopyridine that inhibits the P2Y12 receptor on the surface of thrombocytes. In the TRITON TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction) study,[4] Prasugrel was reported to be superior to Clopidogrel in terms of decreasing ischaemic cardiovascular events, such as myocardial infarction and stent thrombosis, in ACS patients with or without ST-segment elevation (STEMI and NSTE-ACS, respectively) and with a planned invasive procedure, although it was observed to be associated with a higher bleeding risk than Clopidogrel. Also, Prasugrel provides faster, greater and steady platelet inhibition than Clopidogrel. On the other hand, there have been several major adverse events related to Prasugrel such as hypertension, headache and epistaxis. In the TRITON TIMI 38, severe thrombocytopenia has been reported in 17 patients in the Prasugrel arm (0.3%) and 18 patients in the Clopidogrel arm (0.3%).[3] Abnormal hepatic function tests attributed to the use of Prasugrel were observed as uncommon adverse event in post-marketing surveillance. According to the results of "International Consensus Meetings on Adverse Drug Reactions", the under discussion patient had characteristics compatible with "probable" Prasugrel-induced hepatotoxicity due to several reasons: 1) there was no other cause of hepatotoxicity based on normal diagnostic work-up, 2) Prasugrel was the only drug recently administered to this patient, 3) the deterioration in the clinical and laboratory values of the patient continued as long as the drug was given, 4) other drugs were in use for at least one year, without any adverse event, 5) there was no previous history of liver or biliary tract disease. Although several cases of Clopidogrel-induced acute hepatotoxicity have been reported,[5-7] to our knowledge, this is the second reported case to describe the development of hepatotoxicity due to Prasugrel use. The previously reported case was that of a 40-year-old female who developed acute hepatotoxicity after Prasugrel use for acute stent thrombosis, in which an improvement in hepatotoxicity was observed after changing Prasugrel with Clopidogrel.[8]

Although the mechanism underlying Prasugrel-induced hepatotoxicity is exactly unknown, it is most likely to be immunologically mediated and due to hypersensitivity. In the first case of Prasugrel-induced hepatotoxicity, the authors stated that the most likely culprit mechanism was

a hypersensitivity reaction to Prasugrel, which is consistent with the underlying probable cause in our case. Since Prasugrel requires metabolic activation for its antithrombotic effects, occurring in the liver mainly through the cytochrome P450 system, CYP 3A4, and 2B6, another potential mechanism responsible for the Prasugrel-induced hepatotoxicity may be the active metabolite itself and high cytochrome 3A4 activity with cellular glutathione depletion, which have been blamed for the Clopidogrel-induced hepatotoxicity in susceptible persons using Clopidogrel. The rechallenge is frequently considered to be the most trustworthy test for the diagnosis of doubtful cases of drug-induced hepatotoxicity, but it is obviously dangerous and may even result in death. For that reason, we did not carry out the rechallenge test. The severity of Prasugrel-induced hepatotoxicity is typically mild and rapidly reversible with the cessation of therapy.[2,9] Delay in diagnosis can cause serious health problems, including death. In the present case, the severity of hepatotoxicity was high (encephalopathy and high INR). The seriousness of the liver injury observed in this case may be due to the individual's high sensitivity to Prasugrel and uncontrolled diabetes (HbA1c level at 13.5%). Several studies[10-12] showed that diabetes mellitus was an important and independent risk factor for severe hepatotoxicity. Because of the cross-hypersensitivity and structural similarities between Clopidogrel and Prasugrel, Ticagrelor was started, instead of Clopidogrel, after Prasugrel cessation.

Conclusion

Prasugrel-induced hepatotoxicity is a rare but potentially serious adverse effect. This case report illustrates the need to consider hypersensitivity reaction to Prasugrel, via the mechanisms mentioned above, in the differential diagnosis of clinical hepatotoxicity picture. A high degree of clinical suspicion is required in patients presenting with abnormal liver biochemistries after starting prasugrel. Prompt recognition and discontinuation of the offending agent are necessary, as progressive liver injury and even death can occur.

Consent: Consent of the patient was obtained to publish his case.

Disclaimer: None.

Conflict of Interest: None.

Funding Sources: None.

References

1. Al-Abdouh A, Barbarawi M, Abusnina W, Amr M, Zhao D, Savji N, et al. Prasugrel vs Ticagrelor for DAPT in Patients with ACS Undergoing PCI: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Cardiovasc Revasc Med 2020;21:1613-8. doi: 10.1016/j.carrev.2020.05.038.
2. Brunton LL, Knollmann BC, Hilal-Dandan R. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13th ed. In: Shanahan JF, Lebowitz H, eds. New York, USA: McGraw-Hill Education LLC, 2018; pp. 849-76.
3. Husted S, Boersma E. Case Study: Ticagrelor in PLATO and Prasugrel in TRITON-TIMI 38 and TRILOGY-ACS Trials in Patients With Acute Coronary Syndromes. Am J Ther 2016;23:e1876-89. doi: 10.1097/MJT.0000000000000237.
4. Antman EM, Wiviott SD, Murphy SA, Voitk J, Hasin Y, Widimsky P, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. J Am Coll Cardiol 2008;51:2028-33. doi: 10.1016/j.jacc.2008.04.002.
5. Kastalli S, El Aïdli S, Zaïem A, ben Abdallah H, Daghfous R. Fatal liver injury associated with clopidogrel. Fundam Clin Pharmacol 2010;24:433-5. doi: 10.1111/j.1472-8206.2009.00791.x.
6. Ng JA, Goldberg N, Tafreshi MJ. Clopidogrel-induced hepatotoxicity and fever. Pharmacotherapy 2006;26:1023-6. doi: 10.1592/phco.26.7.1023.
7. Beltran-Robles M, Marquez Saavedra E, Sanchez-Muñoz D, Romero-Gomez M. Hepatotoxicity induced by clopidogrel. J Hepatol 2004;40:560-2. doi: 10.1016/j.jhep.2003.11.013.
8. Fernández-Ruiz M, Carbonell-Porras A, García-Reyne A, López-Medrano F. Management of a hypersensitivity reaction to thienopyridines: prasugrel-induced fever and hepatitis resolved after switching to clopidogrel. Rev Esp Cardiol (Engl Ed) 2012;65:773-4. doi: 10.1016/j.recesp.2011.11.011.
9. Scott DM, Norwood RM, Parra D. P2Y12 inhibitors in cardiovascular disease: focus on prasugrel. Ann Pharmacother 2009;43:64-76. doi: 10.1345/aph.1G726.
10. Chatila R, West AB. Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes. Medicine (Baltimore) 1996;75:327-33. doi: 10.1097/00005792-199611000-00003.
11. Torbenson M, Chen YY, Brunt E, Cummings OW, Gottfried M, Jakate S, et al. Glycogenic hepatopathy: an underrecognized hepatic complication of diabetes mellitus. Am J Surg Pathol 2006;30:508-13. doi: 10.1097/00000478-200604000-00012.
12. Koehler EM, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study. Hepatology 2016;63:138-47. doi: 10.1002/hep.27981.