CASE STUDY

An Idiosyncratic Reaction to Clopidogrel

Aaysha Kapila, MD; Lovely Chhabra, MD; Allison Diane Locke, MD; Pranav Patel, MD; Atul Khanna, MD; Chakradhar M Reddy, MD; Mark F Young, MD

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ABSTRACT

Clopidogrel is an irreversible antiplatelet agent belonging to the thienopyridine group that acts to antagonize the adenosine diphosphate P2Y12 receptor on platelets. It thus inhibits the activation of platelet glycoprotein GPIIb/IIIa complex, which is essential for fibrinogen—platelet complex formation. Clopidogrel has widely replaced ticlopidine because of a much better clinical safety profile. Clopidogrel is a prodrug that requires hepatic activation to exert its antiplatelet effect. Hepatotoxicity with use of clopidogrel is a rare but clinically significant phenomenon. We report a case of clopidogrel-induced hepatotoxicity in an elderly white woman.

INTRODUCTION

Clopidogrel is widely used in acute coronary syndrome interventions, for prevention of cerebral thromboembolism, and in neurointerventions such as coil placement in an unruptured aneurysm clipping. Clopidogrel is associated with a wide spectrum of adverse effects, including rash, indigestion, vomiting, diarrhea, thrombotic thrombocytopenic purpura, neutropenia, and aplastic anemia. Hepatotoxicity is an extremely rare and probably underrecognized side effect of clopidogrel. Despite the side effect profile, there are no standard guidelines for follow-up laboratory tests after initiation of clopidogrel. We herewith present the case of a 75-year-old white woman who presented to the hospital with nausea, vomiting, and fever lasting one day. A day before the current presentation, she had undergone an elective anterior cerebral communicating artery aneurysm coiling. Admission laboratory data were consistent with elevated liver enzymes for a mixed hepatotoxic and cholestatic pattern, along with anemia and thrombocytopenia. She had normal laboratory values 5 days before the current admission. Her only new medication, clopidogrel, had been started 5 days before the elective surgery. Viral hepatitis panel and acetaminophen levels were unremarkable. Results of Doppler ultrasound of the right upper quadrant and hepatobiliary iminodiacetic acid (HIDA) scan were normal. Clopidogrel was discontinued and intravenous antibiotics were initiated. The patient's symptoms improved, and bilirubin and transaminases decreased. A postdischarge clinic follow-up revealed complete normalization of hemogram and liver enzymes. Clopidogrel was suspected to be the cause of hepatotoxicity in our patient, as suggested by the temporal correlation of drug therapy. All other etiologies for the liver disease were excluded, and the patient's clinical response to drug withdrawal and rechallenge with medicine confirmed the diagnosis.

CASE STUDY

A 75-year-old white woman underwent an elective cerebral anterior communicating artery aneurysm coiling as empiric intervention to prevent a thrombotic cerebrovascular event. A day after the procedure, the patient presented to the emergency room with an acute febrile illness with symptoms of nausea, vomiting, bloating, and a fever of 38.2°C (100.8°F). She reported that she had been at her baseline health the previous night. She denied any alcohol or acetaminophen usage or any exposure to sick contacts. The patient's only new medication, clopidogrel, had been started 5 days before the elective surgery. She denied any history of gallbladder problems or history of pancreatitis.

The patient's medical history was significant for hypertension, dyslipidemia, degenerative disc disease, and fibromyalgia. Social history was negative for alcohol, smoking, and illicit drug usage. Family history was significant for aneurysms and diabetes. She was allergic to penicillin, which caused anaphylaxis, aspirin, and azithromycin, which caused a rash. Her home medications included esomeprazole, levothyroxine, pregabalin, and risedronate. She had been on these medications for the previous 20 years without any adverse effects.

Her initial vital signs were unremarkable. A comprehensive systemic examination was only remarkable for a mild, diffuse abdominal tenderness without guarding or rigidity. Murphy sign was negative.

Initial blood work, including complete blood count, was significant for a drop in hemoglobin to 11.4 mg/dL (previous value, 13.4 g/dL; normal, 12.4-5.2 g/dL). Hematocrit dropped to 34.9% (normal, 36.0%-46.0%), and platelet count dropped to 114 K/μL (normal, 150-450 K/μL). The differential count for neutrophils was 88% (normal, 45%-75%). Comprehensive metabolic

Aaysha Kapila, MD, is an Internist at East Tennessee State University in Johnson City. E-mail: aaysha.dr@gmail.com. **Lovely Chhabra, MD,** is a Fellow in Cardiovascular Medicine at Hartford Hospital in CT. E-mail: lovids@hotmail.com. **Allison Diane Locke, MD,** is an Internist at East Tennessee State University in Johnson City. E-mail: zads46@goldmail.etsu.edu. **Pranav Patel, MD,** is a Gastroenterologist at East Tennessee State University in Johnson City. E-mail: patelp1@mail.etsu.edu. **Atul Khanna, MD,** is a Gastroenterologist at East Tennessee State University in Johnson City. E-mail: khanna@mail.etsu.edu. **Chakradhar M Reddy, MD,** is a Gastroenterologist at East Tennessee State University in Johnson City. E-mail: chakram_reddy@hotmail.com. **Mark F Young, MD,** is a Gastroenterologist at East Tennessee State University in Johnson City. E-mail: young@mail.etsu.edu.

Table 1. Aspartate aminotransferase/alanine aminotransferase trend, preadmission (Day 0), hospital Day 1 (5 days after initiation of clopidogrel), and Day 14 (on follow-up in primary care physician's office)

	Day 0	Day 5	Day 14
AST (IU/L)	48	1362	62
ALT (IU/L)	32	716	59

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 2. Aspartate aminotransferase/alanine aminotransferase trend after drug rechallenge on days 0, 2, and 7

	Day 0	Day 2	Day 7
AST (IU/L)	49	120	63
ALT (IU/L)	42	92	56

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

panel revealed elevated total bilirubin of 1.6 mg/dL (normal, 0.2-1.1 mg/dL) and a direct bilirubin level of 0.7 mg/dL (normal, 0.0-0.2 mg/dL). Aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels were 1362 IU/L (normal, 15-41 IU/L), 716 IU/L (normal, 14-54 IU/L), and 160 IU/L (normal, 32-92 IU/L), respectively (Table 1). Amylase and lipase were normal. Coagulation profile was normal. Viral hepatitis panel (A, B, C, and E serology) was negative. Serology titers for Lyme disease, Epstein-Barr virus, and cytomegalovirus were negative. Vitamin B_{12} and folate levels were normal. Acetaminophen levels were <10 μg/mL (normal, 10.0-30.0 μg/mL). Results of a standard comprehensive urine and serum toxicology screen were negative. Erythrocyte sedimentation rate was elevated at 22 mm/h (normal, 0-15 mm/h). Blood cultures collected at the time of admission were unremarkable. Urine analysis was significant for urobilinogen levels of 4 EU/dL (normal, <1.0 EU/dL).

Findings from ultrasound of the abdomen and Doppler studies of the portal/hepatic veins were unremarkable. Cholescintigraphy (HIDA scan) demonstrated the gallbladder ejection fraction to be 44% (normal, > 35%). There was no evidence of obstruction involving the cystic duct or the common bile duct.

The patient was initially started on empiric intravenous antibiotics for possible cholangitis. Clopidogrel was withheld after the recommendations from the gastroenterology and neurosurgery teams. Other causes of hepatotoxicity were ruled out by negative viral serology and negative acetaminophen levels, and no underlying liver pathology was evident from the history or the radiologic workup. During hospitalization, the liver enzymes started to trend down as her symptoms resolved.

The patient improved remarkably and was discharged on Day 3 in a stable condition. Antinuclear antibody, anti-smooth muscle antibody, antimitochondrial antibody, and anti-LKM1 antibody tests returned unremarkable results.

The patient was followed up in the primary care office after 2 weeks, and follow-up laboratory tests revealed complete normalization of the liver enzymes (Table 1). After an informed discussion with the patient, she was subjected to a drug rechallenge with a single dose of 75 mg of clopidogrel. Her liver function tests were serially measured on Days 0, 2, and 7, which suggested a worsening pattern of liver enzymes on Day 2, followed by normalizing trend by Day 4, confirming our diagnosis of drug-induced hepatotoxicity (Table 2).

The Maria and Victorino diagnostic scale of hepatotoxicity score was 13, indicating possible drug-induced liver injury. The score for temporal relationship between the drug intake and the onset of the clinical picture was 3 points because the onset of first clinical or laboratory manifestations was less than 8 weeks (5 days). The score for exclusion of alternative causes was 3 points because viral hepatitis, alcoholic liver disease, and biliary tree obstruction were ruled out. The score for extrahepatic manifestation was 2 points, with our patient having fever and anemia on presentation. The score for intentional or accidental re-exposure to the drug was 3 points because the patient recovered on drug rechallenge during hospitalization. The final 2 points were because of cases in the literature associated with clopidogrel.

DISCUSSION

Clopidogrel is widely used for patients with acute coronary syndrome. When combined with aspirin, it is the first-line antiplatelet therapy for decreasing cardiovascular events.[1-3] It is also administered when a stent-assisted coiling placement is envisioned; then, aspirin, 81 mg once daily, and clopidogrel, 75 mg once daily, are given for at least 3 to 5 days before the procedure, or a loading dose of clopidogrel, 300 mg once, may be administered before a procedure.[4]

Clopidogrel is an antiplatelet agent belonging to the thienopyridine class that has widely replaced ticlopidine because of its superior safety profile. It has a wide variety of side effects, the most common being bleeding, diarrhea, rash, indigestion, nausea, and vomiting.[5] It is also associated with more severe adverse reactions like pancytopenia, thrombotic thrombocytopenic purpura, hepatotoxicity, serum sickness, and systemic inflammatory response syndrome.[6-13]

In terms of hepatotoxicity, the most common observation was a mixed hepatocellular and cholestatic pattern, with three cases of isolated hepatocellular injury and one of cholestatic injury.[14] Review of the literature suggested only a few cases of hepatotoxicity caused by clopidogrel.

Clopidogrel undergoes activation by hepatic metabolism by CYP3A4 and CYP3A5. Simultaneous administration of CYP3A4 inhibitors like ketoconazole was shown to prevent the metabolism and reduce the toxicity of clopidogrel. High CYP3A4 activity is an important risk factor for induction of clopidogrel-induced hepatotoxicity.[15]

The mechanism of clopidogrel-induced liver injury is either direct dose-dependent toxicity or dose-independent

idiosyncratic hypersensitivity reaction.[8,16] Our patient had onset of symptoms within five days of initiation of the medication, probably indicating a hypersensitivity mechanism. The patient's other home medications were a stable regimen for years. Secondly, the patient received the anesthetic propofol, which has been very rarely associated with hepatitis; when it is associated with hepatitis, a hepatocellular pattern is more prevalent.[17] However, a supporting drug dechallenge and a positive drug rechallenge highly favor the diagnosis of clopidogrel-induced hepatotoxicity.

Our patient had resolution of symptoms and improvement of liver function within 24 to 48 hours of the discontinuation of the medication. Even though acute liver injury is rare with clopidogrel, it is important for clinicians to recognize that this medication is potentially hepatotoxic. Thus, it should be used with caution in patients with underlying liver disease and should be discontinued if signs of jaundice or overt liver failure are observed. ❖

Learning Points

1. Clopidogrel is an irreversible platelet inhibitor that can cause adverse reactions ranging from mild gastrointestinal intolerance to more severe reactions, such as pancytopenia, thrombotic thrombocytopenic purpura, hepatotoxicity, serum sickness, and systemic inflammatory response syndrome.
2. Clopidogrel can induce hepatotoxicity either by a direct dose-dependent phenomenon or by a dose-independent idiosyncratic hypersensitivity reaction.
3. Clinicians should be vigilant and consider discontinuing clopidogrel if the patient develops signs of jaundice or liver failure.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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The Price Tag

The human's "desire to take medicine" carries, however, a price tag.
Nature's maladies are succeeded by iatrogenic hazards.

— Kurt Kroenke. Polypharmacy. Causes, consequences, and cure. Am J Med 1985 Aug;79(2):149-52