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Case Report

Clopidogrel Induced Hepatic Toxicity

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Abstract

A 57 year old female presented to the Emergency Department (ED) with nausea, vomiting and abdominal pain which had worsened since hospital discharge for an non-ST elevation myocardial infarction (NSTEMI) less than 24 hours ago. In the ED, it was noted her liver function tests were extremely elevated (AST=1157 IU/L, ALT=1253 IU/L, and Alkaline Phosphatase=116 IU/L) and further imaging revealed no abnormal hepatic disease or aortic dissection. The patient had been started on clopidogrel, aspirin, promethazine and nitroglycerin 3 days prior to her current ED visit due to the new NSTEMI. She had taken 2 doses each of clopidogrel and aspirin with no difficulties noted during her first hospital stay. The patient was admitted from the ED with hepatic toxicity; subsequently treated with fluid resuscitation over the next 48 hours and possible offending agents were held (atorvastatin and clopidogrel). She was followed with serial liver function tests, which revealed a downward trend and her symptoms of nausea, vomiting and abdominal pain completely resolved over the following 2 days. The medical team agreed that her newly added clopidogrel was the likely cause of her acute liver injury. Clopidogrel induced liver toxicity is reported as a post marketing adverse event in the Plavix® package insert, but only 15 patients worldwide (with 3 US cases) are located in the literature. Although this adverse event appears to be rare, it has been fatal in several cases. Prompt diagnosis of acute hepatic injury with discontinuation of clopidogrel and addition of supportive care may reverse this rapid deterioration of liver function.

Keywords: Clopidogrel; Acute liver injury; Hepatotoxicity

Abbreviations

ED: Emergency Department; ALT: Alanine Transaminase; AST: Asparate Aminotransferase; CT: Computed Tomography; NSTEMI: Non-ST-Elevation Myocardial Infarction; mg: Milligrams; IU/L: International Units per Liter; mcg/hr: Micrograms per Hour; ml/hr: Milliliters per Hour; CYP450: Cytochrome P450; ADP: Adenosine Diphosphate; MI: Myocardial Infarction; CABG: Coronary Artery Bypass Graft; ADP: Adenosine Diphosphate; ADR: Adverse Drug Reaction; PCP: Primary Care Physician

Case Presentation

A 57 year old white female with documented normal liver function and no history of alcohol abuse, liver or biliary tract disease presented to the emergency department (ED) with worsening nausea and vomiting over the past 24 hours. She reported associated dizziness, coldness and pain in her back, which subsequently moved to her chest, left shoulder and bilateral legs. Labs were obtained revealing ALT=1253 IU/L, AST=1157 IU/L and Alkaline Phosphatase=116 IU/L. A right upper quadrant ultrasound was obtained which showed no abnormal liver disease. There was a concern for dissection due to patient's complaint of abdominal pain, so a CT (computed tomography) chest was obtained that revealed no retroperitoneal hemorrhage or abdominal aortic aneurysm. She was admitted to the inpatient family medicine service to investigate the cause of her acute liver injury.

The patient was discharged approximately 24 hours prior to the ED visit after being hospitalized for 2 days with a new onset non-ST-elevation myocardial infarction (NSTEMI). During this previous admission, she underwent a left heart catheterization and was found to have no significant occlusive disease that required stenting. Laboratory results obtained the morning following her heart catheterization revealed normal liver function tests (reported in table 1 as baseline results). Cardiology recommended the addition of clopidogrel 75 mg daily and aspirin 81 mg daily to the patient's medical regimen. The clopidogrel and aspirin were ordered and the patient received two doses of each medication while hospitalized. The patient was discharged with 4 new medications to her regimen: clopidogrel 75 mg daily, aspirin 81 mg daily, promethazine 12.5 mg every 4 hours as needed for nausea, and nitroglycerin 0.4 mg as needed for chest pain. Before returning to the hospital, she attempted to take promethazine at home, but was not successful in keeping the tablet down to control her nausea. Nitroglycerin was not given prior to her arrival at the ED.

The patient's past medical history included hypertension, diverticulosis hyperlipidemia, osteoarthritis, spinal enthesopathy, and the new onset NSTEMI 2 days prior to the ED visit. Her current medications included metoprolol tartrate 25 mg twice a day, carisoprodol 350 mg every 8 hours as needed, vitamin D3 2000 IU at bedtime, atorvastatin 20 mg at bedtime, fentanyl 50 mcg/hr patch every 72 hours, lisinopril 10 mg daily, and the recent additions of aspirin, clopidogrel, promethazine and nitroglycerin. Her chronic medications (minus the new additions) were stable and had not been changed or adjusted in over 6 months.

The patient's newly started clopidogrel and long term atorvastatin were both discontinued upon admission. She was treated with aggressive fluid resuscitation over the next 2 days, receiving normal saline at 250 ml/hr for 13 hours followed by normal saline at 150 ml/hr for approximately 30 hours. During this time, her liver function tests

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Table 1: Patient Liver Enzymes.

	Baseline-- 54 hours prior to Adverse Drug Reaction (ADR)	Day 1-1800	Day 2-0652	Day 2-0925	Day 3-0630	Day 3-0904	Day 6-Primary Care Physician (PCP) follow up	2 month PCP follow up
ALT (IU/L)	32	1253	755	633	427	441	159	26
AST (IU/L)	54	1157	427	376	143	142	26	24
AlkPhos (IU/L)	66	116	88	84	93	98	94	80
Total Bilirubin (mg/dl)	0.6	0.8	0.8	0.7	0.5	0.7	0.7	0.4
Lipase (units/L)		19						

were monitored closely, showing a nice downward trend (see Table 1). A hepatitis panel was also obtained on admission, which resulted in nonreactive results for Hepatitis A, B and C. Her medication list was examined closely for drug-drug interactions, but no interactions (specifically no CYP450 interactions) were found within her current pharmacotherapy regimen. With normalization of liver enzymes using only fluid resuscitation and withdrawal of possible offending agents, clopidogrel was identified as the likely causative agent of the liver injury due to the very recent addition of this medication. The patient's nausea and vomiting subsided and she was ready for discharge on day 3. She was discharged on her original medication list (including the atorvastatin) minus the clopidogrel, as cardiology recommended no other thienopyridine therapy for at least 2 weeks. At 3 days post hospital follow up with her primary care physician, the liver enzymes had all trended toward normal and patient reported feeling well. At 2 months following this adverse drug event, the liver enzymes had all returned to normal with no complaints from the patient.

Discussion/Conclusion

Clopidogrel is a non-reversible thienopyridine that inhibits platelet aggregation by its action on the $P2Y_{12}$ receptor. After a two-step metabolism by CYP450 (mainly CYP2C19) enzymes to an active metabolite, clopidogrel blocks the adenosine diphosphate (ADP) receptor on the platelet surface, reducing the ability of the platelets to bind together for the remainder of the life of the platelet (7-10 days) [1].

Clopidogrel has been widely studied for a variety of antiplatelet uses and is currently recommended in several of the American College of Cardiology Foundation/American Heart Association treatment guidelines. Clopidogrel (with aspirin) is recommended as a first line antiplatelet agent for medically managed NSTEMI patients [2]. In the 2012 update of the guidelines, ticagrelor is also included as an alternative to clopidogrel for medically managed NSTEMI patients (post diagnostic angiography) due to the PLATO study. Ticagrelor was shown to be superior to clopidogrel, with a 16% relative reduction in the composite endpoint of vascular death, MI or stroke at the end of 12 months, showing no difference in either the invasive or conservatively managed patient. However, ticagrelor's superiority was diminished by the higher rate of non-CABG related major bleeding (4.5% vs. 3.8%, p=0.03) [3]. Thus, the use of clopidogrel and aspirin in combination for antiplatelet therapy in NSTEMI patients is commonly seen in clinical practice.

The rapid development of acute liver injury following the new start of clopidogrel led to a second hospitalization for this patient. Using the Naranjo ADR probability scale [4], a score of 7 can be calculated for this patient case. This gives a probable association of clopidogrel and the noted acute hepatitis. The Maria and Victorino validated scale for drug induced hepatic injury [5] was also applied to this case. This scale yielded a result of 13 {temporal relationship (7), exclusion (3), extra hepatic manifestations (1), re-exposure (0), previous reports of drug-induced injury by medication (2)}, indicating clopidogrel is possibly involved in this case of liver injury. Although neither of these scores gives a definitive answer regarding the involvement of clopidogrel in this patient, her rapid recovery of liver enzymes and cessation of nausea following discontinuation of this medication was enough evidence to link the two events without any question by the medical team.

Acute liver injury is reported as a possible adverse event only in the post marketing surveillance per the Plavix® package insert, but incidence or numbers related to this adverse effect are not given [1]. Drug induced hepatitis from clopidogrel is not commonly reported in the medical literature and was not seen in healthy volunteers [6]. A search of PubMed and Google Scholar using the terms "hepatitis", "drug induced liver injury" and "clopidogrel" resulted in only 15 published case reports over 10+ years of clinical use. Goyal and colleagues developed a summary table of patient characteristics with clopidogrel induced liver injury, which includes the 13 case reports published prior to 2009 [7]. Since that time, two other case reports have been published [8,9], bringing the total to 15, with only 3 of these reports coming from the United States. With the addition of this case report, the grand total is now only 16 patients who have experienced this rare adverse effect out of the over 28 million annual prescriptions written for clopidogrel [10]. A review of all case reports [7-9,11-22] shows that patients were age 50-89, roughly equal male and female (7 vs. 9 respectively) and on clopidogrel for 2-180 days prior to the development of the drug induced hepatitis. Very few patients (4 of 16) were subjected to a re-challenge test for this adverse event due to ethical reasons, and most patients recovered without further incident. However, 2 of the 16 patients suffered a fatal outcome from the hepatic injury. Even though this adverse event with clopidogrel is rare, surveillance by practitioners with early detection of liver injury and prompt discontinuation of the medication are vital for optimal patient outcomes.

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