Clopidogrel-induced liver damage: A case report and review of the literature

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Abstract

The patient was a 78 year old man who had undergone thrombolysis and angioplasty LAD.. After 45 days, he returned to the clinic with icterus, after detailed work up,suspecting clopidogrel induced liver injury, the clopidogrel was substituted with ticagrelor. icterus and laboratory abnormality was relieved in 2 weeks.

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Key Clinical Message

liver toxicity is a rare adverse effect of clopidogrel. because clopidogrel is widely used in cardiovascular problems, and as this complication is reversible, it is of great importance to consider this adverse effect and manage it appropriately.

Background

The liver has a major role in the elimination and excretion of many drugs, which can sometimes lead to chemical damage. Epidemiologic studies have revealed that 1 in every 1000 individuals suffers from drug-induced liver injury (DILI) (1); this damage can vary from mild lab abnormalities to acute liver failure (2,3). Clopidogrel is an anti-platelet medication from the Tinopyridine group which is [commonly] used to prevent clot formation in coronary, cerebral and peripheral vascular diseases and has led to decreased mortality and reinfarction in patients with acute coronary syndrome. It is considered relatively safe therapeutically, but liver injury has rarely been reported after administration. Except two reported cases of cholestasis [alone], liver injury due to clopidogrel has been in the form of a hepatocellular or mixed cholestatic/hepatocellular pattern 94, 5, 6). In this case report, an individual with severe liver injury due to clopidogrel is assessed and there is also a literature review.

Case Presentation

The patient was a 78 year old man who had successfully been treated by thrombolysis (Alteplase, Boringer-Ingelheim) before undergoing angiography and angioplasty on the LAD with a drug eluting stent the next day.

His only risk factor for coronary disease was a previous history of smoking. Echocardiography demonstrated the following results:

EF=25-30%,LARGE LV CLOT (16*7 mm2) in apex,no significant valvular disease

The patient was discharged in a stable condition with normal lab findings and prescribed the following medications:

Tab ASA 80 mg/daily,tab Clopidogrel 75mg/daily(sanofi),tab carvedilol 6.25BD,Tab captopril25 mg BD,tab pentoprazol 40 mg/daily ,tab warfarin 5mg /daily

At the time of discharge, the following lab data were noted;

Wbc=10200 (4.5 -10.8 $\times$ 10^9/L) ,Hgb=14.5 g/dl,plt=290,000,AST=135 u/l(10-42),ALT=37 u/l(7-45),Bilirubin µmol/lit (total=1.2,direct=0.3),cr=1.05 mg/dl

40 days after angioplasty, the patient returned complaining of icterus, itching and decreased appetite. The patient had no recent history of fever, abdominal pain, weight loss, nausea, vomiting, urine or stool discoloration or bleeding from any site in the body. He had no history of using OTCs, herbal remedies or alcoholic beverages. In the physical exam, the vital signs were stable and the patient did not appear ill or toxic. None of the stigmata of chronic liver disease were observed; the abdomen was soft and there was no sign of ascites or organomegaly. Cardiac and neurological examinations did not reveal any abnormalities.

A gastrointestinal consultation was requested for the patient and further tests were conducted as shown in table-1

Immunologic and serological tests for hepatitis A, B, C and E and tumor markers were negative (table 1); abdominopelvic ultrasound showed no lesions and subsequent MRCP displayed normal size and shape of the intrahepatic and extrahepatic biliary tracts as well as normal wall thickness and appearance of the gall bladder, without any lesions or filling defects. The pancreatic ducts were normal.

Based on the lack of anatomical lesions, a diagnosis of liver injury with a hepatocellular, cholestatic or mixed pattern due to autoimmunity or, more probably, drug-induced, was considered. Bearing in mind the patient's most recent echocardiography, which had shown relatively improved cardiac function without the presence of clots in the left ventricle (EF=35%) , medications were discontinued based on their likelihood to cause liver damage, so statins were discontinued initially, followed by captopril and, lastly, warfarin. Despite these measures, no improvement in the lab findings or the patient's jaundice was observed and there was actually an increase in the bilirubin level.

Bilirubin (total=13,direct =8.8),AST=130,ALT=250

After [witnessing] the rise in bilirubin, clopidogrel was substituted by ticegralor; subsequently, over the next two weeks, the patient's jaundice improved and the lab results returned to normal.

Bilirubin (total=1.05,direct=0.7),AST=41,ALT=52,Alkaline Phosphatase=141

Medications other than clopidogrel were restarted gradually with 1 week intervals in between and over a follow-up period of two months, normalization of the lab data and his general condition was observed.

Discussion

Clopidogrel is highly effective in the treatment of cardiovascular disease, but occasional side effects, such as rash, gastrointestinal problems and bleeding. Have been reported after its administration. In recent years, some researchers have cited hepatotoxic side effects related to this drug (7,8); more specifically, 20 such cases have been reported in the literature (table 2). In most of these investigations, the average age of the patients was approximately 68 (34-90) years and the average time between the observation of side effects and the initiation of clopidogrel [therapy] was 35 (3-180) days; these figures are consistent with our findings. In the literature, the most common pattern of liver damage was mixed (11 cases), while 5 cases showed solely hepatocellular involvement and two displayed only cholestatic injury (5,9,10) . Most studies

have indicated the survival of the majority of patients and improvement of lab results within 1 week to 6 months of discontinuing the medication. In our presented case, improvement of lab findings took 2 weeks. To our knowledge, there has only been a single death reported due to the hepatotoxic side effects of clopidogrel (11).

The exact cause of liver injury due to clopidogrel remains undetermined, but two possible mechanisms consisting of a direct dose-dependent reaction or an idiosyncratic non-dose-dependent reaction have been suggested (12).

In our case, hepatotoxicity was observed 1 month after the initiation of clopidogrel; he demonstrated no signs of hypersensitivity, such as rash, arthralgia or eosinophilia and the clinical presentation pointed [more] towards a dose-dependent reaction.

Clopidogrel is a prodrug converted to its active form, which consists of MERCAPTO group, by various cytochromes in the liver, including CYP 4A3 and CYT P 450 (12) . These active metabolites are responsible for the anti-platelet effects as well as the hepatotoxic effects of the medication due to inhibition of cell glutathione. Medications that stimulate CYP 4A3, such as rifampin, can increase the harmful effects of clopidrogrel on the liver; moreover, one significant finding on biopsies carried out by various investigators was that the greatest damage was observed in zone 3 of the liver, which indicates the potential involvement of CYT P 450 in the pathogenesis of liver injury. The inhibition of the cytochrome P 450 isoenzyme by clopidogrel is dependent on time, dosage and NADPH. Drugs such as captopril, hydrochlorothiazide and allopurinol can lead to cholestasis via this pathway. By affecting some isoenzymes in the cytochrome P 450 and CYP 4A3 pathways, interactions between clopidrogrel and omeprazole or certain statins, such as atorvastatin, may lead to liver damage (14).

In summary, due to the widespread use of clopidrogrel in various diseases, it is prudent to bear in mind the less common side effects of this medication, particularly when there is a possibility of drug interaction.

Table 1. Patient's lab data

Bilirubin (μmol/lit)	Total (6.1),direct(5.7)*
ALT (U/L)	266*(7-45)
AST (U/L)	122* (10-42)
GAMA GT (U/L)	930(11-50)*
ALK PHOSP (IU/L)	545(40-130)*
ALBUMIN (g/Dl)	4 g/dl (3.5 to 5.5)
IgG(SERUM) mg/dl	1230(700-1600)
INR	2.7
IgG 4 SUBCLASS (mg/dl)	80(4-86)
AMA-M2	NEGATIVE titer less than 1:40
SERUM TOTAL IgG (mg/dl)	12.61(7-16)
IgM (mg/dl)	0.87(0.4-2.3)
FANA	NEGATIVE
Serum protein electrophoresis Hepatitis A HBS Ag HCV Ab Hepatitis E CEA CA19-9	NORMAL NEGATIVE NEGATIV

Table 2. Side effects related to clopidorgrel based on the literature.

Reference	**Age**	**Days at onset**	**Liver injury pattern**	**Outcome**
Willens et al (2000)	81	21	Mixed	Recovered

Duran Quintana et al (2002)	77	180	Mixed		Recovered
Ramos Ramos et al (2003)	89	60	Mixed		Recovered
Batwaet al (2003)	57	3	Hepatocellular		Recovered
Beltran-Robles et al (2004)	59	4	Hepatocellular		Recovered
Chau et at (2005)	74	37	Mixed		Recovered
Höllmülleret al (2006)	80	43	Mixed		Recovered
Ng et al (2006)	59	3	Hepatocellular		Recovered
Lopez-Vincente et al (2007)	63	30	Mixed		Recovered
Wiper et al (2008)	56	60	Mixed		Recovered
Goyal et al (2009)	78	33	Mixed		Recovered
Kastali et al (2010)	63	19	Mixed		Died
Monteiro et al (2011)	80	30	Hepatocellular		Recovered
Pegram et al (2014)	57	3	Hepatocellular		Recovered
Kapila et al (2015)	75	5	Hepatocellular		Recovered
Pisapia et al (2015)	53	3	Mixed		Recovered
Etxeberria-Lekuona et al (2016)	78	3	Cholestatic		Recovered
Keshmiri et al (2016)	34	135	Hepatocellular		Recovered
Current case	74	30	Cholestatic	c	Recovered

Author Contribution:

Dr Azin Gheimati has been as the pharmacotherapy consultant during the patient managent and has reviewed the article,and doctor Vahid Eslami has been the responsible physician of the case and has written the article.

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