JSTMU Journal of Shifa Tameer-e-Millat University

https://j.stmu.edu.pk

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SHORT COMMENTARY

Overlooked hepatotoxicity with Clopidogrel

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Author`s Contribution

[1]Draft, Idea, Approval

Article Info.

Conflict of interest: Nil

Funding Sources: Nil

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Cite this article as: Malik J. Overlooked hepatotoxicity with clopidogrel. JSTMU. 2020; 3(2):132-133.

A B S T R A C T

Clopidogrel is an adenosine diphosphate receptor blocker. It is widely used as a part of dual antiplatelet therapy (DAPT) in patients with ischemic heart disease (IHD), regardless of the acute coronary syndrome (ACS). Although a rarely reported entity, clopidogrel-induced liver injury is commonly seen in clinical practice. It is widely overlooked by clinicians and is thus a potential hazard to patients with IHD.

Keywords: *Drug-induced liver injury, clopidogrel-induced hepatotoxicity, p2y12 inhibitor side effects*

Clopidogrel is an inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation. It acts by direct inhibition of ADP on its receptor and the subsequent ADP-mediated activation of glycoprotein GPIIb/IIIa complex. It is a pro-drug, which metabolizes into an active form in the liver cytochrome complex (CYP1A2, CYP2C19, CYP3A4) leading to the inhibition of platelet aggregation.[1] The association between the liver metabolism and pharmacokinetics of Clopidogrel was studied in two sub-studies of clinical trials (Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY-TIMI 28) and Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndrome (TRITON-TIMI 38).[2,3] The active metabolites of Clopidogrel inhibit the binding of ADP selectively to its P2Y12 receptor, thereby inhibiting platelet aggregation. All the steps in this metabolism are irreversible. As a consequence, platelets exposed to the drug's active metabolite are affected for their life span in the body.

Various large-scale trials have shown that clopidogrel decreases major adverse cardiovascular events (MACE) in patients with acute coronary syndromes. Its role is pivotal in medically treated subsets of ACS and it is considered to be an adjunct to aspirin after percutaneous coronary intervention (PCI). The clinical evidence of the efficacy of clopidogrel is demonstrated in four clinical trials involving 81,090 patients: The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE); Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE); The Clopidogrel and Metoprolol in Myocardial Infarction/Second Chinese Cardiac Study (COMMIT/CCS-2) and The CLARITY-TIMI 28.[4-6]

Food and drug administration (FDA) has deemed Clopidogrel as safe as aspirin due to its low-risk side-effect profile and positive clinical feedback for the past two decades. The most common adverse effects are gastrointestinal discomfort, easy bruisability, pruritus, and increased bleeding. Other more serious, but rare effects are immune thrombocytopenic purpura (ITP), aplastic anaemia, hemolytic-uremic syndrome (HUS), and severe hypersensitivity.[7]. Acute liver injury leading to liver failure is very rarely defined in the literature. It was added later in the post-marketing surveillance in the Plavix® (Clopidogrel) package insert. Clopidogrel is associated with elevation of liver enzymes in no less than 5% of the patients after initiating the treatment. It can take from 24 hours to 24 weeks (on average 6 weeks) for the liver injury to set in.[8] Although fulminant hepatic failure is only defined in two case reports, in clinical practice, it is more commonly seen than it is reported. The usual pattern of liver enzyme elevation is hepatocellular, but cases with cholestatic or mixed pictures of jaundice are also reported. The mechanism of injury is unknown but several

reviews have hypothesized an idiosyncratic immunologic reaction with the complex hepatic metabolism of the Clopidogrel molecule.[9] There is a susceptibility of drug-drug interaction of Clopidogrel with agents that exhibit an interplay with the cytochrome complex., specifically the CYP2C19 allele. Among various wild type alleles of CYP2C19, *17 allele is associated with increased activity while an allele which encodes two or more non-functional phenotypes are called poor metabolizers of the drug. This is hypothesized to cause the liver injury.[10]

In a routine cardiology clinic (Rawalpindi Institute of Cardiology), we see a multitude of cases with no apparent cause for elevated liver enzymes or jaundice other than drug-induced liver injury (DILI). They are only suspected of having an adverse response to initiation of clopidogrel but due to the non-progressive course of this hepatocellular damage, it is often overlooked by the clinicians. It usually acts like a 'scrub-sink' of learning at our institute but dissemination to the global audience is lacking. This conduct is partially due to the paucity of literature on this subject. To date, only 15 case reports have been documented on clopidogrel-induced hepatotoxicity. In the existing literature, it has been shown that the idiosyncratic liver injury is not related to the presence of pre-existing liver abnormalities.[8] This is usually a diagnosis of exclusion and there are no validated scores to label DILI. However, several case reports have used Maria and Victorino and/or Roussel Uclaf causality assessment method (RUCAM) scale successfully in diagnosing clopidogrel-induced liver injury.[11]

For clinicians and specialists working in cardiology, they must be updated regarding the DILI score systems. The importance of a review of the literature on this subject cannot be emphasized for every future and practising cardiologist. Apart from development of diagnostic biomarkers, it would be feasible to sensitize our fellow clinicians about the various DILI scales and refinement of the parameters to incorporate the relevant items for an acceptable level of diagnosis.

Conclusion

In conclusion, the RUCAM and Maria and Victorino scales should be adopted for the comprehensive assessment of the causal association of Clopidogrel and liver injury. Moreover, clinical trials must be initiated to scientifically prove the mechanisms behind clopidogrel-induced liver injury and degree of hepatocellular damage.

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