Hepatotoxicity of Combined Therapy of Atorvastatin with Platelet $P2Y_{12}$-ADP Receptor Antagonist in Coronary Heart Disease Treated Patients

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ABSTRACT :

BACKGROUND:

Clopidogrel, an adenosine diphosphate receptor blocker, is widely used as an adjunctive antiplatelet therapy in coronary disease and percutaneous coronary stenting. It appears to be a safe drug with few occurrences of liver side-effects that usually resolved after drug withdrawal**.**

OBJECTIVE:

The goal of this study was to investigate whether the co-administration of atorvastatin could aggravate the hepatic - toxicity of clopidogrel.

PATIENTS AND METHODS:

Eighty patients with coronary disease were included in this study. All patients received a dose of 75 mg/day of clopidogrel. Forty patients group A with recent treatment (< 3 months) of clopidogrel; other forty patients group B with (> 1 year) treatment of clopidogrel. Liver function tests were measured and studied at baseline (clopidogrel without atorvastatin) and at 2, 4, 6 weeks of clopidogrel with atorvastatin (40 mg/day) afterwards.

RESULTS:

Liver function tests with co-therapy showed high significant elevation in mean serum total alkaline phosphatase ($P<0.001$), significant decrease ($P< 0.05$) in mean serum gamma-glutamyl transferase ,significant elevation ($P< 0.05$) in mean serum direct bilirubin and insignificant elevation ($P>0.05$) in mean serum total bilirubin , whereas the results appeared within normal range in mean serum levels of alanine aminotransferase, aspartate aminotransferase ,glutamate dehydrogenase -1,and total protein .

CONCLUSION:

Combination of atorvastatin and clopidogrel may induce hepatic injury cholestatic type resulting from abnormal bile flow caused by either drugs or its metabolites.

KEYWORDS: clopidogrel; atorvastatin; liver function tests.

INTRODUCTION:

The use of percutaneous coronary intervention as an alternative to coronary artery bypass graft surgery has expanded dramatically in the past two decades. Per procedural death, myocardial infarction, and vessel occlusion are the major complications following balloon angioplasty. They are due to arterial thrombus formation at the site of mechanical plaque disruption and distal embolization of platelet thrombi into the coronary circulation [12]Antiplatelet therapy is an important adjunctive treatment that reduces ischemic complications in patient undergoing percutaneous coronary intervention .The thienopyridine derivative, clopidogrel, produce an irreversible inhibition of the platelet adenosine diphosphate receptor, and thereby attenuate platelet aggregation in response to adenosine diphosphate released from activated platelets.[13]The PCI-CURE study [1] showed that clopidogrel, in addition to aspirin, before and continued beyond the standard course of 4 weeks after percutaneous coronary intervention was superior to placebo in preventing major ischemic events. [2,3] they report a case of hepatotoxicity associated with the use of clopidogrel in a patient undergoing coronary artery stenting. Although most trials assessing the cardio vascular efficacy of statins and their safety have included a large number of patients, they have been under-powered to detect clinically relevant drug-induced liver injury (DILI) . The

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idiosyncratic DILI associated with drugs is generally detected in the post-marketing phase [4]. It has been convincingly shown that the risk of developing statin-induced DILI is not related to the presence of pre-existing liver abnormalities, mostly non-alcoholic fatty liver disease (NAFLD) [5] . On the contrary, the use of statins has been shown to be associated with improvement in liver test abnormalities and histology in patients with NAFLD[6, 7].

PATIENTS AND METHODS :

Eighty patients, (30 female, 50 male), their ages ranging from (50-75) year, with coronary heart diseases recruited from the Ibn Albitar Center for Cardiac Surgery. Diagnoses are made based on clinical symptoms and tests like Electrocardiogram (ECG), Echocardiogram stress test and Coronary angiography. Patients with liver disease , renal failure, and heart failure have been excluded. According to the duration of clopidogrel (75mg /day) treatment, forty of patients (group A) presented with recent treatment(<3 months), other forty (group B) presented with (> 1 year) treatment, starting therapy with single daily dose of clopidogrel 75 mg followed by the addition of atorvastatin 40mg once daily. Blood samples are aspirated on 2 week intervals starting from day-0 (Baseline), day-15 ,day-30 and day-45 to measure liver function tests that assayed by Photometric Colorimetric Test ,serum glutamate dehydrogenase-1 assayed by the quantitative sandwich enzyme immunoassay technique (ELISA).

RESULT: Baseline characteristics of 80 patients were taken and showen in Table 1-. The results of this study revealed that the mean levels of serum direct bilirubin, in group A and B at 15,30-days were significantly increase (P< 0.05) compared with the upper normal range while mean levels of serum total bilirubin in group A and B were insignificantly change (P> 0.05) . The results of mean serum alanine aminotransferase (ALT) ,aspartate aminotransferase (AST), glutamate dehydrogenase (GLUDH-1) and total protein showed changes within the normal range at follow up time study. The result of mean levels of serum alkaline phosphatase (ALP) for group A and B at the baseline time and at co therapy time showing highly significant increase (P< 0.001) compared with upper normal range. The result of mean levels of serum gamma-glutamyltransferase (γ-GT) for group A and B at the baseline time showing highly significant increase (P< 0.001) compared with the upper normal range, whereas at co-therapy intervals insignificant change (P>0.05) observed in both groups compared with the upper normal range.

DISCUSSION:

The statistical results of liver function tests revealed that clopidogrel therapy at the baseline causes highly significant elevation (P<0.001) of mean serum total alkaline phosphatase (>1.45 x ULN, upper limits of normal) for both groups , highly significant elevation (P<0.001) in mean serum gamma-glutamyltransferase (> 1.56 x ULN) for both groups and insignificant increase (P>0.05) in mean serum direct bilirubin levels for both groups , while the mean serum levels of alanine aminotransferase, aspartate aminotransferase and mitochondrial glutamate dehydrogenase -1 (GLUDH-1) for both groups were within the normal range .According to CIOMS patterns of drug induced liver injury (DILI), the pattern of liver injury caused by clopidogrel in this study was cholestatic type. DILI is divided into three types: hepatocellular, cholestatic, and mixed according to the Councils for International Organizations of Medical Sciences (CIOMS) [14] .Hepatocellular type is defined by alanine aminotransferase (ALT) > 2 x ULN or R ≥ 5, where R is the ratio of serum activity of ALT/serum activity of alkaline phosphatase (ALP), both of which are expressed as multiples of the ULN. Cholestatic type is defined by ALP > 2 x ULN or R ≤ 2 and mixed type is defined by ALT > 2 x ULN and 2 < R < 5. Patients with cholestatic/ mixed type are likely to develop chronic disease more frequently than those with hepatocellular type [11]. DILI has a wide spectrum of manifestations, ranging from asymptomatic mild biochemical abnormalities to severe hepatitis with jaundice. In most cases of DILI, liver injury would be expected to improve following discontinuation of the drug suspected to be responsible. On the other hand, some DILI patients may even show resolution of liver injury without discontinuation of the drug. Therefore, it should be carefully evaluated whether the suspected drug should be discontinued with adequate consideration of the importance of the medication.Although there are no definitive criteria for cessation of the suspected causative drug, the FDA, Food and Drug Administration, proposed draft guidelines in which ALT > 8 × ULN at any one time , ALT > 5 × ULN for two weeks, ALT > 3 × ULN in association with serum bilirubin >2 x ULN, PT-INR (prothrombin time- international normalized ratio) > 1.5 ×ULN , or symptoms of liver injury should be used to predict severe hepatotoxicity and recommend discontinuing the drug [15].The mechanism of clopidogrel hepatotoxicity is

still unclear but it is more likely to be non-dose dependent, either due to direct toxicity by hypersensitivity immunological mechanism or by a metabolic Idiosyncratic process, dependent upon individual susceptibility, or due to indirect toxic effect that may occur as a result of interactions with other drugs metabolized by cytochrome P450 isoenzymes [10]. In the current study, the addition of Atorvastatin (40 mg/day) co-treatment with Clopidogrel (75 mg /day) caused highly significant elevation in mean serum alkaline phosphatase ($P<0.001$) for group A and B at all follow up intervals, while the mean serum GGT level for groups A & B noted significant decrease ($P<0.01$) and ($P<0.05$) respectively at day-15 and a high significant decrease ($P<0.001$) at day-30 and 45 compared with baseline mean of each groups. However, Co-treatment therapy caused significant elevation ($P<0.05$) in mean serum direct bilirubin level and insignificant elevation ($P>0.05$) in mean serum total bilirubin for groups A & B. The co–treatment therapy of this study will cause decrease elevated level of mean serum total alkaline phosphatase of statin and decrease elevated level of mean serum GGT of clopidogrel and will not cause liver cell necrosis or hepatocellular injury. Atorvastatin is mostly associated with cholestatic liver injury than hepatocellular injury (Calderon *et al.,* 2010). Atorvastatin-induced cholestatic injury was proven by rapid improvement with cessation of the drug and recurrence with re-initiation of atorvastatin. The duration between exposure and on set of toxicity varies, ranging from 12 hours to 52-weeks [16] .In hepatocellular injury, the transaminase elevations are frequently dose-dependent and occur in the first 16 weeks of therapy. Moreover, most of the ALT elevations observed were clinically asymptomatic and showed spontaneous reduction indicating that transient ALT elevation poses little risk for the development of major hepatotoxicity due to statin treatment [17]. Statins may have pleiotropic effects on the improvement of hepatic dysfunction, as suggested that atorvastatin significantly reduced serum GGT concentrations [9] . GGT is a microsomal enzyme present in hepatocytes and biliary epithelial cells, as well as in extra hepatic tissue such as the renal tubules, pancreas, and intestines [18].The primary role of GGT is to transfer glutamyl group of GSH to amino acid to be transport across the cell membrane, increase oxidative stress lead to depletion of GSH and increase GGT levels. Statins persistently lowered serum GGT levels may reflect reduced oxidative stress, thus reducing damage to hepatocytes and bile ducts [8]

Table 1:Distribution of the patients in the study groups.

	Group –A	Group -B	P-value
Number (n)	40	40	NS*
Mean age (year), ± SD (Range)	60 ± 15 (45–75)	63 ± 13 (50–75)	NS*
Female sex %	42.5 %	32.5 %	NS*
Male sex %	57.5 %	67.5 %	NS*
Hypertension, %	75 %	80 %	NS*
Diabetes mellitus, %	30 %	35 %	NS*
Hypercholesterolemia, %	50 %	55 %	NS*
Unstable angina %	25 %	25 %	NS*
Stable angina %	25 %	25 %	NS*
NSTEMI %	30 %	30 %	NS*
STEMI %	20 %	20 %	NS*
Drug Eluting Stent (DES %)	67 %	70 %	NS*

NS* = Non-significant difference; $P>0.05$,
NSTEMI = Non-ST segment elevation myocardial infarction
STEMI = ST segment elevation myocardial infarction

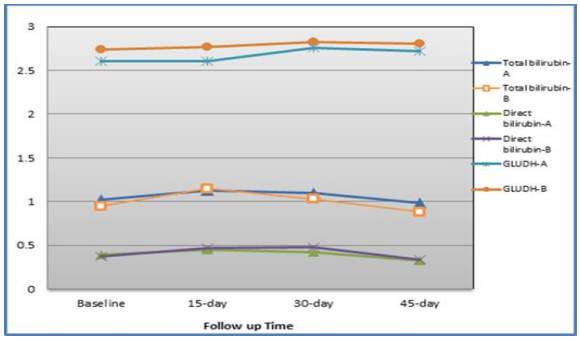

Figure 1:The mean serum total and direct bilirubin and glutamate dehydrogenase -1(GLUDH1) level for study groups.

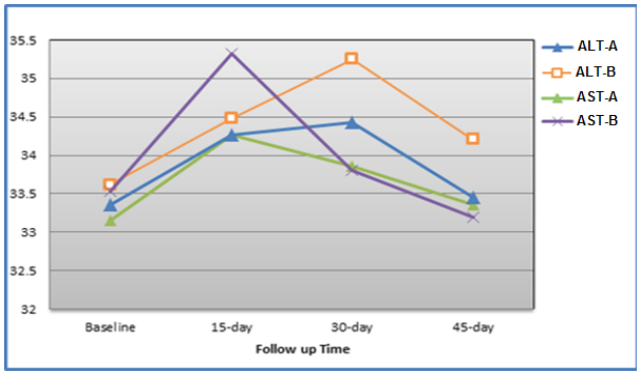

Figure 2 :The mean serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) level for study groups.

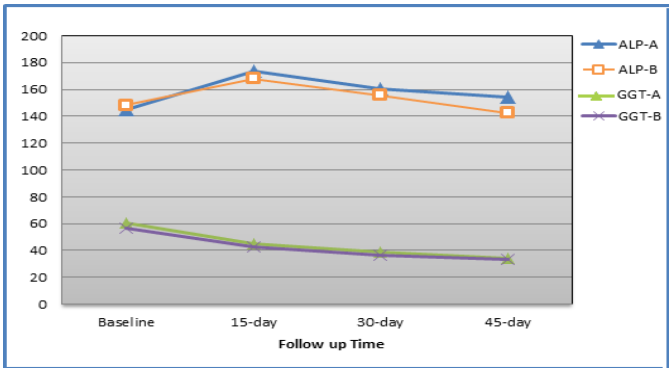

Figure 3: The mean level of serum gamma glutamyltransferase (GGT) and alkaline phosphatase (ALP) for study groups.

Table 2:The mean levels of serum liver function tests for study groups.

		Baseline (B)	day-15	day-30	day-45
1-Mean S.total Bilirubin (mg/dl) ± SD	-Group-A	1.02 ± 0.43	1.13 ± 0.57	1.1 ± 0.55	0.98 ± 0.47
	P-value *vs.* B	------	NS*	NS*	NS*
	-Group-B	0.95 ± 0.6	1.15 ± 0.56	1.03 ± 0.45	0.88 ± 0.48
	P-value *vs.* B	------	NS*	NS*	NS*
2- Mean S.direct Bilirubin (mg/dl) ± SD	-Group-A	0.39 ± 0.38	0.45 ± 0.32	0,42 ± 0.36	0.33 ± 0.25
	P-value *vs.* B	------	P< 0.05	P< 0.05	NS*
	-Group-B	0.37 ± 0.35	0.47 ± 0.42	0.48 ± 0.34	0.34 ± 0.3
	P-value *vs.* B	------	P< 0.05	P< 0.05	NS*
3- Mean S.ALT (IU/L) ± SD	-Group-A	33.36 ± 4.4	34.27 ± 4.3	34.43 ± 4.8	33.45 ± 4.2
	P-value *vs.* B	------	NS*	NS*	NS*
	-Group-B	33.62 ±4.5	34.48 ± 4.8	35.25 ± 5.4	34.21 ± 5.3
	P-value *vs.* B	-----	NS*	NS*	NS*
4-Mean S.AST (IU/L) ± SD	-Group-A	33.15 ± 4.8	34.26 ± 4.4	33.86 ± 4.3	33.36 ± 4.5
	P-value *vs.* B	------	NS*	NS*	NS*
	-Group-B	33.53 ± 5.2	35.32 ± 4.8	33.8 ± 4.7	33.2 ± 5.3
	P-value *vs.* B	------	NS*	NS*	NS*
5- Mean S. GLUDH-1 (IU/L) ± SD	-Group-A	2.624 ± 0.45	2.755 ± 0.36	2.719 ± 0.32	2.657 ± 0.46
	P-value *vs.* B	-----	NS*	NS*	NS*
	-Group-B	2.735 ± 0.42	2.827 ± 0.32	2.803 ± 0. 30	2.768 ± 0.38
	P-value *vs.* B	-----	NS*	NS*	NS*
6- Mean S. ALP (IU/L) ± SD	-Group-A	145.16 ± 40.5	173.73 ± 33.4	160.5 ± 43.28	154.46 ± 32.6
	P-value *vs.* B	-----	P< 0.005	P< 0.05	NS*
	-Group-B	148.08 ± 35.4	168.12 ± 40.3	155.73 ± 43.2	150.3 ± 30.6
	P-value *vs.* B	------	P< 0.005	P< 0.05	NS*
7- Mean S. γ-GT (IU/L) ± SD	-Group-A	60.22 ± 20.3	45.26 ± 21.3	38.5 ± 19.5	34.3 ± 18.5
	P-value *vs.* B	------	P< 0.01▼	P< 0.001▼	P< 0.001▼
	-Group-B	56.34 ± 19.6	42.8 ± 20.4	36.33 ± 18.62	33.7 ± 17.8
	P-value *vs.* *B*	------	P< 0.05▼	P< 0.001▼	P< 0.001▼

NS* = Non-significant difference, P>0.05 ; *vs.*=*versus* ; Baseline=(day-0)

CONCLUSION:

Combination of atorvastatin and clopidogrel may induce hepatic injury cholestasis type resulting from abnormal bile flow caused by either drugs or its metabolites. Treatment with atorvastatin significantly reduced elevated level of serum GGT in patients with clopidogrel therapy.

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