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Is Acute Hepatocellular Injury By Statins, A Class Effect?

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ABSTRACT

Hepatotoxicity is one of the primary causes of Acute liver failure. It is rarely encountered because of its low incidence and lack of research. Pharmaceutical preparations are currently serious contributors to hepatotoxicity. Susceptibility factors that predispose the individuals to drug induced liver injury have not been identified. An unabridged instrument should be made for evaluation of drug induced hepatotoxicity. We present a case report of a 49 year old male, a case of unstable angina who developed signs of idiosyncratic hepatocellular injury in response to Atorvastatin 80mg. His liver enzymes had strikingly elevated, which resolved on withdrawal of the drug. No other concomitant drugs taken by the patient could attribute to this phenomenon. The patient was then prescribed with Rosuvastatin 10mg per day for cardiovascular risk reduction after a temporary statin free period. This demonstrated a lack of class effect on statin induced hepatotoxicity. Although many case reports are available on statin induced transaminitis, this case report stands out due to the presence of clinically significant symptoms of Acute hepatocellular injury, strikingly elevated liver enzymes and positive outcome with a switch over to another statin.

Keywords: Hepatotoxicity, Atorvastatin, Acute liver failure

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INTRODUCTION

Statins are widely prescribed class of drugs due to the Cardiovascular risk reduction property, by lowering cholesterol levels in the body. Statins inhibit HMG-CoA(3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase, which is a rate limiting step in cholesterol biosynthesis. It is effective in lowering low density lipoprotein cholesterol (LDL-C) levels by 20-50 percentage and triglyceride levels by 10-20% and raising high density lipoprotein cholesterol (HDL-C) levels by 5 -10 % (1). Common side effects of statins include muscle symptoms, nausea, sleep disturbances, rash, etc. The clinical significance of statin induced transaminases is uncertain as the vast majority of patients are asymptomatic. Atorvastatin is the major drug among statins which is associated with hepatotoxicity. It occurs by induction of caspase activity, triggering of apoptosis, reduction of coenzyme Q 10 and by the generation of free radicals. (2)

CASE REPORT

Day 1: A 49 year old male patient, a private employee, of weight 63kg came to General medicine department. The patient had a past medical history of Diabetes Mellitus for 7 years. He presented with chest pain which was crushing type, radiating to back without sweating palpitation or dyspnoea which was relieved by rest. On initial examination, he was conscious and oriented. His Blood Pressure had risen to 130/70 mmHg. Electrocardiogram showed biphasic T waves. Angiogram revealed mild Left Anterior Descending Artery myocardial bridging. He was diagnosed as having unstable angina. He was provided with supportive measures like low molecular weight heparin 60mg, Tablet Pantoprazole 40 mg and Tablet Lorazepam 1 mg.

Day 2:Patient felt better and had no chest pain. Laboratory investigations showed elevated Fasting Blood Sugar of 195 mg/dl and elevated lipid profile while other liver function tests were normal. He was started on Tablet Aspirin 75 mg OD, Tablet Clopidogrel 75mg OD, Tablet Ramipril 2.5mg OD, Tablet Atorvastatin 80mg OD, Syrup Lactulose 15 ml HS, Tablet Pantoprazole 40mg OD, Tablet Glyceryl Trinitrate 2.6mg OD, Tablet Gliclazide 40mg OD while continuing Low molecular weight Heparin 60mg

Day 3: Patient was asymptomatic. Laboratory investigation showed mildly elevated liver enzymes. The same drugs were continued.

Day 4: Patient suffered from nausea.

Day 5: Patient had right upper quadrant pain and nausea. Laboratory investigation showed strikingly elevated liver enzymes, about 25 times greater than the upper normal limit. Tablet Atorvastatin 80 mg was withheld.

Day 6: The severity of patient's abdominal pain reduced. Liver function tests showed lower levels of enzymes

Day 7: Patient's symptom reduced. Liver function test showed further reduction in liver enzymes

Day 8:Patient was asymptomatic and was discharged after observation for one day. The discharge medications involved all the routine drugs except Atorvastatin. The patient was advised to report to the physician immediately in case of any symptom and asked to review after 2 weeks.

On First Review (after 2 weeks):Patient was asymptomatic. Laboratory investigation showed normal levels of liver enzymes. He was prescribed with Rosuvastatin 10 mg daily and was advised to report to the physician in case of any symptom.

On Second Review(After 1 month):Patient was stable. Laboratory investigations were normal and the patient was asked to continue the same routine drugs.

Table 1: Abnormal Liver Enzymes

Liver enzymes	Day 1	Day 3	Day 5	Day 6	Day 7	First Review (After two weeks)	Second Review (After one month)
Serum glutamic pyruvic transaminase(U/L) Ref: (5 - 38)	34	60	1090	439	173	39	36
Serum glutamic oxaloacetic transaminase (U/L) Ref: (5 - 41)	37	21	1420	321	104	35	32
Alkaline Phosphatase (U/L) Ref : (40 -129)	51		56			55	

DISCUSSION

Statins are lifesaving therapy for patients with hypercholesteremia and other risk factors for cardiovascular diseases. Drug induced liver diseases are generally detected in the post marketing phase. Statin induced hepatotoxicity is usually called a myth and is controversial. The use of statins has proved to improve liver function tests. Idiosyncratic liver injury with statin are rare, but occurs with severe outcome. The risk of developing liver injury by statins has not been associated with the presence of pre-existing liver abnormality including Non-alcoholic fatty liver disease. Atorvastatin and Simvastatin are the drugs mostly associated with hepatotoxicity among statins, partly due to the fact that these are the most widely used statins. Mild elevations in liver enzymes occur in approximately 1-3 % population on statins, but are not clinically significant.(3)

Maximal recommended dosage of Atorvastatin is associated with a modest but notable increase in transaminases which resolves on continuing the therapy (4). Our patient had a significant increase in transaminases right from day one, but did not resolve on continuation of the therapy. Elevation in liver enzymes occur only in 0.1-2.7% upto three times the upper limit of normal values and is rarely associated with clinical symptoms (5,6).Our patient's liver enzymes had risen upto 25 times the upper normal limit and the patient had experienced upper right quadrant pain and nausea. The recovery time of hepatotoxicity was within 1-3 months (7) which is in line with our patient's recovery which was 2 weeks.

The abnormal liver enzyme level and abdominal pain had a reasonable time relationship to intake of Atorvastatin 80 mg. It cannot be attributed to other concomitant drugs as apart from atorvastatin, only Aspirin had the potential to cause hepatotoxicity but only at high anti-inflammatory doses. The liver enzymes reverted to normal on withdrawal of Atorvastatin. Causality assessment was done with WHO (World Health Organization) causality assessment scale and the adverse drug reaction was classified as probable.

As Biopsy was not cost effective for the patient, the liver injury was diagnosed as Idiosyncratic Acute Hepatocellular injury from the Laboratory data, as ALP was within normal limits, whereas SGPT and SGOT were greater than 5 times the normal limit (8). The usual term 'transaminitis' was not used because our patient had clinical manifestations as well.

A study showed that Drug induced liver injury was associated with advanced age and higher dose(3,6).It was partly in line with our case where Atorvastatin was given at a high dose of 80mg, but the patient was a middle aged man. Liver related symptoms generally occur at 4 weeks after initiation of the statins (9). But our patient experienced symptoms from day one of initiation. Studies show that elevation in liver enzymes is transient and resolves spontaneously in 70% cases, if the same drug and dose is continued (10,11).

Switching to a lower dosage of a more potent statin like Rosuvastatin 10mg per day is recommended for high risk patients (9). After withdrawal of Atorvastatin, our patient was on a statin free period for 2 weeks and was later prescribed with Rosuvastatin 10 mg daily. There are rare chances of hepatotoxicity on switching to another statin, so it is to be done with caution and careful monitoring.

Animal studies suggest, the depletion of mevalonate or one of its sterol metabolites by HMG CoA reductase enzymes may be responsible for statin induced hepatotoxicity (12). The hepatocytes usually adapt to the drug by activation of adaptation pathways such as nuclear factor erythroid 2-related factor 2(Nrf2), a prime regulator of antioxidant defense (13). Dietary factors

such as proteins, low or high content of lipids, Vitamin D ,alcohol and genetics have also been found to influence the tolerability of patients to statins.

CONCLUSION

Satins act as a cornerstone in clinical settings to prevent cardiovascular deaths in the population. It is important to establish a sound assessment of statin induced hepatotoxicity from a large clinical data, including different sects of the population in the post marketing phase. Hepatotoxicity induced by statins can be a barrier to maximize cardiovascular risk reduction. Physicians should perform liver function tests in patients who develop new symptoms like nausea, vomiting or abdominal pain while on statins.

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