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Cardiology

STATIN INDUCED RHABDOMYOLYSIS

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ABSTRACT Statins are group of medicines that lower the level of low-density lipoprotein (LDL) cholesterol. They may exert toxic effects on skeletal muscle ranging from simple muscle pain to life-threatening complications such as rhabdomyolysis. We report a case of 74-year-old male who was prescribed statins along with other drugs for treatment of coronary artery disease (CAD) and developed rhabdomyolysis which lead to acute renal failure. Treatment was initiated with immediate discontinuation of statin followed by hemodialysis. Statin induced rhabdomyolysis is very rare nearly 0.1%. We report this case as the usage of a statin group of drug resulted in acute kidney injury and improved with discontinuation of drug along with few sessions of hemodialysis.

KEYWORDS : Acute kidney injury, Creatinine Phosphokinase, Statin, Rhabdomyolysis

INTRODUCTION:

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statin drugs, have been studied in numerous controlled human research trials involving hundreds of thousands of study participants. Based on this vast research and clinical experience, statins have been shown to improve lipid blood levels and reduce atherosclerotic coronary artery disease (CAD) risk, resulting in reduced CAD morbidity and mortality, and in several studies, reduced overall ("all-cause") mortality.[1] Statin therapy has been proven both safe and well tolerated in millions of patients over nearly 15 years of clinical use. The main adverse effects of statins include dyspepsia, gastrointestinal disturbances, headaches, myalgia, central nervous system disturbances, and sleep disorders. The more clinically significant adverse events that deserve attention include hepatotoxicity and skeletal muscle abnormalities like rhabdomyolysis.[2] Myalgia is the most common side effect of statin use, with documented rates from 1-10%. Whereas, rhabdomyolysis is the most serious adverse effect from statin use, though it occurs quite rarely (less than 0.1%).[3]

Rhabdomyolysis is a clinical syndrome that results from severe and widespread injury to skeletal muscle and the subsequent accumulation of toxic muscle products in the blood and urine. It is accompanied by findings such as myoglobinuria, myoglobinemia, and evidence of target-organ damage, such as decreased renal function or acute renal failure.[4] The mechanism by which statins cause myopathy is not completely understood. Evidence from well designed randomized controlled trials shows that myopathy correlates most closely with dose of statins and is independent of reductions in low density lipoprotein cholesterol.[5] Several risk factors have been proposed, mainly by experts on the basis of published evidence as shown in Table 1.[6,7]

Table 1 Factors that may increase the risk of statin induced myopathy

Advanced age (>80 years old)
Female sex
Low body mass index
Multisystem diseases (for example, diabetes mellitus)
Diseases affecting kidney or liver function
Hypothyroidism (untreated)
Drug interactions (for example, fibrates, nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, thiazolidinediones, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin)
Vigorous exercise
Excess alcohol
Intercurrent infections
Major surgery or trauma
Diet (excessive grapefruit or cranberry juice)
Genetic factors (for example, polymorphisms of the cytochrome P450 isoenzymes or drug transporters, inherited defects of muscle metabolism, traits that affect oxidative metabolism of fatty acids)

Case Report:

A 74yr old man admitted with complaint of breathlessness, sudden in onset of one day duration which was present even on walking for a short distance (NYHA III). There was no history of chest pain, palpitations or any syncope. He reported that he was known diabetic for past fifteen years and was on treatment with oral hypoglycemic agents (not specified). There were no other co-morbid illnesses and no prior history of similar complaints in the past. He did not report history of any substance abuse.

On examination, there were no signs of pallor, cyanosis or edema. His vitals were essentially normal. There was a gallop rhythm on auscultation of heart and further examination of chest revealed bibasilar crepitations. His electrocardiogram showed normal axis and a pathological 'q' wave in inferior leads along with T wave inversions. On further evaluation, his 2D echo was consistent with ECG findings and showed a regional wall motion abnormality in RCA and LAD territory (anterior wall, mid basal inferior wall hypokinetic). He had mild LV dysfunction and his left ventricular ejection fraction was 45%. These findings were further confirmed by angiography.

His biochemical profile was normal other than his glucose levels which showed elevated fasting and post prandial values. Hemogram and other investigations were in normal range.

Patient was started on anticoagulants, antiplatelets and atorvastatin 80mg on day 1 followed by 40mg thereafter. On day 8 of his stay in hospital he became drowsy and complained of not passing urine for a duration of six hours. He also complained of generalized myalgia and it was observed that his urine was reddish brown in color. Creatinine phosphokinase (CPK) was 8190 IU/L (reference upper limit of normal range- 170 IU/L). His blood urea and serum creatinine were increased compared to the baseline values.

Based on these findings a diagnosis of rhabdomyolysis secondary to statin usage was established. Statins were stopped immediately and he was started on hemodialysis. There was dramatic improvement in his CPK levels, renal profile (Table 2) and his urine output. He was discharged a few days later with prescription of Ezetimibe 10mg once daily.

TABLE 2

	Day 10	Day 11	Day 12	Day 13	Day 16	Day 17	Day 19
Serum urea	158	223	180	158	206	156	115
Sr. creatinine	5.1	7.1	5.1	5.8	3.6	2.4	1.6
CPK	-	8260	4560	-	2665	400	-
HD	2nd HD	3rd HD	-	4th HD			

DISCUSSION:

Since their introduction for the treatment of hypercholesterolaemia in 1987, the use of statins has grown to over 100 million prescriptions per year.[8] Lovastatin was the first commercial statin which was given FDA approval in September 1987.[9] The reported rates of serious adverse events (SAEs) among statins as a class have been very low (<1%).[10]

The US Food and Drug Administration Adverse Event Reporting System database reports rates of statin-induced rhabdomyolysis of 0.3–13.5 cases per 1,000,000 statin prescriptions.[11] Although initially defined by the US Food and Drug Administration (FDA) as a CK level greater than 10 000 U/L,[4] more recently rhabdomyolysis has been defined by the FDA as an appropriate diagnosis only when organ damage (typically renal insufficiency) occurs in association with elevated CK levels.[12] In this case CPK was elevated to 8190 IU/L (nearly 50 times) which did not satisfy the early criteria for rhabdomyolysis, but there was evidence of organ damage in the form of acute kidney injury which was satisfying recent definition as per FDA.

Drug-drug interactions with statins are significantly more likely to be associated with myopathy this is because statins are extensively metabolized via cytochrome P450 (CYP) pathways. Lovastatin, simvastatin, atorvastatin, and cerivastatin use mainly the CYP3A4 pathway. The concurrent use of statins that are recognized by CYP3A4 and other agents that are potent inhibitors or substrates of this enzyme—in particular, the azole antifungals, some macrolide antibiotics, and cyclosporine lead to increased toxicity of the drugs. However, it should be noted that the risk for myopathy also appears to increase when statins are combined with drugs that may not be metabolized via the CYP3A4 pathway, such as fibrates and niacin.[12] This interaction was unlikely in our case as there was no concomitant use of above mentioned drugs.

The time between initiation of statin to onset of rhabdomyolysis was 8 days in this case which is similar to a case series[13] with a mean duration of 9 days. Acute kidney injury is a potential complication of severe rhabdomyolysis, and the prognosis is substantially worse if renal failure develops.[14] Although the exact mechanisms by which rhabdomyolysis impairs the glomerular filtration rate are unclear, experimental evidence suggests that intrarenal vasoconstriction, direct and ischemic tubule injury, and tubular obstruction all play a role.[15] Development of acute kidney injury was very rapid in our case occurring almost simultaneously with myalgia.

The standards of care for rhabdomyolysis- induced acute kidney injury include, aggressive intravenous fluids until myoglobinuria is cleared, urine alkalization if urine pH<6.5, maintaining urine output at rate of 200ml/hour and renal-replacement therapy if there is oliguria or anuria, symptomatic hyperkalemia, volume overload and resistant metabolic acidosis.[14] Continuous venovenous hemofiltration or hemodiafiltration has shown some efficacy in removing myoglobin.[16] The use of antioxidants and free-radical scavengers (e.g., pentoxifylline, vitamin E, and vitamin C) may be justified in the treatment or prevention of myoglobinuric acute kidney injury, but controlled studies evaluating their efficacy are lacking.[17]

CONCLUSION:

Statin-associated myopathy should be suspected when a statin-treated patient complains of unexplained, generalized muscle pain, tenderness, or weakness. Likewise, patients should be taught to recognize symptoms of myopathy and report them promptly. If myopathy is suspected, statin therapy should be discontinued and serum CK levels should be monitored. Early diagnosis and treatment of symptomatic CK elevations, including cessation of drug therapies potentially related to myopathy, can prevent the progression to rhabdomyolysis.

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