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Early Statin Myotoxicity Causing Rhabdomyolysis and Acute Renal Failure: A Case Report

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Abstract: ***Statins are a class of medicines employed to reduce low-density lipoprotein cholesterol. However, beyond their established lipid-lowering role, they can produce skeletal-muscle toxicity along a continuum, from uncomplicated myalgia to severe, life-threatening rhabdomyolysis. The present case report outlines a 66-year-old man who was initiated on statin therapy, in conjunction with other agents for coronary artery disease, and subsequently developed rhabdomyolysis complicated by acute renal failure. The cornerstone of management was immediate cessation of the statin, followed by hemodialysis. Statin-induced rhabdomyolysis is distinctly uncommon, with an estimated occurrence of approximately 0.1%. In this patient, renal injury improved after withdrawal of the implicated drug and a few sessions of hemodialysis, underscoring the importance of early recognition and timely intervention when such rare but serious toxicity is suspected in routine cardiovascular practice.***

Keywords: Statin-induced myopathy, Rhabdomyolysis, Acute kidney injury, Hemodialysis

1. 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)

2. Case Report

A 66-year-old man was admitted with **sudden-onset breathlessness of one day's duration**, limiting even minimal exertion and consistent with **NYHA class III dyspnoea**. There was **no history of chest pain, palpitations, or syncope**. He was a **known diabetic for 20 years**, treated with **oral antidiabetic agents** (specific drugs not documented). No other comorbid illness, prior similar episodes, or substance abuse was reported.

On examination, he was **hemodynamically stable**, without pallor, cyanosis, or peripheral oedema. Cardiac auscultation revealed a **gallop rhythm**, and respiratory examination demonstrated **bibasilar crepitations**, in keeping with pulmonary congestion. The **electrocardiogram** showed a **normal axis** with **pathological Q waves in the inferior leads** and **T-wave inversions**. **Two-dimensional echocardiography** revealed **regional wall motion abnormalities** involving the **RCA and LAD territories** (anterior wall and mid-basal inferior wall hypokinesia) with **mild left ventricular systolic dysfunction** and an **ejection fraction of 40%**. These findings were further corroborated by **coronary angiography**, confirming **coronary artery disease**. Baseline laboratory evaluation was reported as normal except for **elevated fasting and postprandial glucose values**. The patient was commenced on **anticoagulants, antiplatelet agents, and high-intensity statin therapy (atorvastatin 80 mg)**.

During the hospital course, he subsequently developed features suggestive of **rhabdomyolysis with acute kidney injury**, for which **haemodialysis** was initiated and serial biochemical monitoring was performed. The **table-based** trend of renal indices and muscle enzyme levels is as follows:

On **Day 9**, serum urea was **184 mg/dL** and serum creatinine **4.8 mg/dL**, and the **first haemodialysis session** was administered. On **Day 10**, serum urea increased to **202 mg/dL** and creatinine to **5.9 mg/dL**; **CPK was 9,880 IU/L**, and the **second haemodialysis session** was performed. On **Day 11**, serum urea further rose to **245 mg/dL** and creatinine to **6.9 mg/dL**; **CPK remained markedly elevated at 8,530 IU/L**, and a **third haemodialysis session** was given. By **Day 12**, serum urea decreased to **167 mg/dL** and creatinine to **5.1 mg/dL**, accompanied by a substantial fall in **CPK to 3,780 IU/L**. On **Day 14**, serum urea was **144 mg/dL** and creatinine **4.2 mg/dL**, and a **fourth haemodialysis session** was recorded. On **Day 15**, serum urea was **150 mg/dL**, creatinine **3.4 mg/dL**, and **CPK 2,674 IU/L**. By **Day 18**, serum urea declined further to **124 mg/dL** with creatinine **2.9 mg/dL**, and **CPK had nearly normalized to 380 IU/L**. On **Day 21**, serum urea was **115 mg/dL** and serum creatinine **1.6 mg/dL**, indicating substantial recovery of renal function.

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.

	Day 9	Day 10	Day 11	Day 12	Day 14	Day 15	Day 18	Day 21
Serum urea	184	202	245	167	144	150	124	115
Sr. creatinine	4.8	5.9	6.9	5.1	4.2	3.4	2.9	1.6
CPK	-	9880	8530	3780	-	2674	380	-
HD	1st session	2nd session	3rd session	-	4th session			

3. 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]

4. 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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