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ATORVASTATIN INDUCED RHABDOMYOLYSIS WITH ACUTE KIDNEY INJURY: CASE REPORT

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Abstract

Hyperlipidemia, commonly managed with statins, is a significant contributor to cardiovascular morbidity. While statins are generally safe, the rare complication is rhabdomyolysis, characterized by severe muscle breakdown, poses a serious risk. This case report presents a 48- years old male with a history of ischemic heart disease and recent coronary angioplasty, who developed rhabdomyolysis attributed to atorvastatin (Tab. Tonact). The patient exhibited symptoms of myalgia, weakness, and alarming laboratory abnormalities, leading to acute kidney injury. Utilizing the naranjo scale, the adverse drug reaction was deemed "Probable." The discussion explores the spectrum of statin-induced myopathy, risk factors, and proposed mechanisms. Management involved statin discontinuation, intravenous hydration, and monitoring for improvement. The patient's recovery was complicated by fever and renal complications, ultimately diagnosed as rapidly progressive renal failure. This case underscores the importance of vigilance in statin use, considering risk factors and promptly addressing myopathy symptoms. Clinicians should be aware of alternative lipid-lowering strategies and potential complications, emphasizing the need for patient education and comprehensive risk assessments. The report concludes with recommendations for future statin therapy and underscores the necessity for careful monitoring in high-risk individuals.

Key words: Rhabdomyolysis, Statin, Probable, Myopathy, Naranjo scale

Introduction

Hyperlipidemia stands out as a significant contributor to cardiovascular morbidity and mortality. Statins, specifically 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, take precedence as the primary treatment for dyslipidemias and play a central role in preventing Atherosclerotic Cardiovascular Disease (ASCVD)[1.] The extensive use of statins for coronary artery disease prevention has been well-established through large randomized trials, showcasing both their effectiveness and generally acceptable safety profile. However, it's crucial to acknowledge the rare but severe complication of statin therapy-rhabdomyolysis. This condition, the most extreme form of myotoxicity, can manifest with any statin, either in isolation or in combination therapy, leading to the breakdown of striated muscle fibres and the release of myoglobin into the blood circulation, accompanied by a tenfold increase in creatine kinase levels beyond the normal range[3.]

Despite their widespread use and proven efficacy since their introduction in 1987, statins are not without potential risks. While statins are generally considered safe, the occurrence of rhabdomyolysis is a recognized, albeit rare, adverse effect[2 5]. The prevalence of severe statin-induced myopathy remains low, affecting less than 1% of patients taking statins[4.] According to reports from the US FDA adverse event reporting system database, the rate of statin induced rhabdomyolysis is estimated to be between 0.3 and 13.55 cases per 1,000,000 prescriptions[6.]

In a six month double blind randomized control study involving 420 healthy volunteers, findings indicated that 9.4% of those receiving daily atorvastatin at an 80 mg dose experienced myalgia, compared to 4.6% among the placebo group.[1] It is essential to distinguish between benign muscle pain without biochemical abnormalities and severe myopathies, where discontinuation of statin use becomes imperative, and active therapy might be necessary.[2]

Case report

A 48 years old male patient was hospitalized in the male medical ward with chief complaints of generalized body weakness for the past 5 days, black-colored stools, and hematuria (red-colored urine). He also reported a history of fatigue and bleeding per rectum. The patient had a chronic pattern of alcoholism, a persistent tobacco chewing habit, and was a known case of Ischemic Heart Disease. He underwent percutaneous transluminal coronary angioplasty a month ago and had been on medications (Tab. Prax-A 75/10, Tab. Tonact 40, Tab. Nikoran 5mg) since then.

All necessary investigations were conducted, revealing elevated levels of CPK (>8000 IU/L), SGPT (558 IU/L), SGOT (1955 IU/L), blood urea (76 mg/dl), sr. creatinine (2.0 mg/dl), uric acid (8.2 mg/dl), and Sr. Phosphorous (7.1 mg/dL). Urine analysis indicated albuminuria and granular casts. CBC showed features of megaloblastic anemia with decreased Hb (11.2), PCV (33.1), MCV (78.3), MCH (26.4), and increased RDW (16.3). Neutrophil levels were elevated (88.8), while lymphocytes were decreased (7.4), suggesting a possible infection or inflammation.

Based on the history, clinical findings, and laboratory reports, the patient was diagnosed with rhabdomyolysis and suspected kidney problems. Tab. Tonact was discontinued, and the patient received intravenous fluids (normal saline), Syp. Looz for constipation, Anobliss cream for rectal bleeding, and continued Tab. Prax-A75/10 and Tab. Nikoran 5mg. On the second day, blood urea (111 mg/dl), Sr. creatinine (2.5 mg/dl) and potassium (5.8) levels increased. A nephrologist was consulted, who suspected acute kidney injury, ordered USG of abdomen and KUB, added Tab. Co Q and Tab. Sobisis, and initiated a treatment plan with Inj. Lasix, Inj. Calcium gluconate, and strict monitoring of the I/O chart. This treatment continued for three days.

The patient later complained of fever, myalgia, and abdominal pain, with further increases in Sr. creatinine (3.9) and Sr. potassium (6). Calcium polystyrene sulphate powder (K bind sachets) was added to remove extra potassium. USG of abdomen and KUB revealed increased bilateral renal cortical echogenicity, suggestive of renal parenchymal disease. The nephrologist suspected rapidly progressive renal failure

(RPRF), prescribed Tab. Acidose and Tab. Cefokem for 8 days. Symptomatic treatment included painkillers, multivitamins, B-protein powder, and DVT stockings for 24 days. With gradual improvement in the patient's condition and laboratory values, he was discharged with medications (Tab. Co Q 10 mg twice daily, Tab. Prax-A75/10mg once daily, Tab. Nikoran 5mg twice daily, Syp. Cremaffin at night, and B-protein powder for 7 days). The patient was instructed to review after 7 days with CBC, RFT, LFT, and total CK reports for further follow-up.

Table-1 Assessment of causality for suspected adverse drug reaction using Naranjo scale

[Definite: >= 9 or greater, Probable: 5-8, Possible: 1-4, and doubtful: 0]

Sl. No.	Question	Yes	No	Don't know/NA	Score
1	Are there prior conclusive reports on this reaction?	+1	0	0	+1
2	Did the adverse event occur after the suspected drug was administered?	+2	-1	0	+2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4	Did the adverse event reappear when the drug was re-administered?	+2	1	0	0
5	Are there alterative causes (other than the drug) that could independently have caused the reaction?	-1	+2	0	+2
6	Did the reaction reoccur when a placebo was given?	-1	+1	0	0
7	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9	Did the patient have a similar reaction tonthe same or similar drugs in any previous exposure?	+1	0	0	0
10	Was the adverse event confirmed by any objective evidence	+1	0	0	+1
Total					+7

In this case the suspected ADR is "Probable" type of ADR as per Naranjo scale assessment

Discussion

The most significant adverse reactions associated with statins involve the elevation of myopathy and rhabdomyolysis, characterized by extensive muscle necrosis, myoglobinuria, and acute renal failure[7]. Statins are commonly acknowledged as safe and effective medications for managing hyperlipidemia. They operate by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, preventing the conversion of HMG-CoA to mevalonate, a precursor of cholesterol and coenzyme Q10 (CoQ10). Statin related myotoxicity can manifest as myalgia (muscle pain), myositis (inflammation and CPK elevation), and rhabdomyolysis (myositis with CPK elevation and renal insufficiency).[8]

The clinical spectrum of statin-induced myopathy spans from myalgia, myositis, and rhabdomyolysis to asymptomatic increase in concentration of creatine kinase (CK). Symptoms include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping, and tendon pain. [1, 6] Onset of symtoms can occur between 1 to 60 days of initiating statin therapy. [6, 9] Various risk factors for precipitating myopathy encompass advanced age, female sex, low body mass index, diminished hepatic and renal function, multiple comorbidities (such as untreated hypothyroidism, diabetes, etc.), medications, excess alcohol, intercurrent infections, surgery or trauma, drug interactions, and dietary factors. [8, 9] This can lead to life-threatening complications such as acute renal failure, disseminated intravascular coagulation, and Hyperkalemia[4].

The mechanism of statin induced myopathy is remains unkown[10]. Several proposed theories include impaired cholesterol synthesis leading to changes in myocyte membrane cholesterol and behavior, impaired synthesis of compounds in cholesterol pathyway (specifically deficiencyof coenzyme Q10), and depletion of isoprenoids preventing myofibril apoptosis. Pharmacodynamic factors, such as transporters affecting statin bioavailability, likely play a role in determaining toxicity, although no directevidence has been found in humans. In vitro and in vivo experiments suggest that lipophilic statins (e.g. Simvastatin, atorvastatin, lovastatin) are more likely to produce muscular effects than relatively hydrophilic agents (e.g pravastatin, rosuvastatin, and fluvastatin). Lipophilic compounds have a greater tendency to penetrate

muscle tissue, enhancing the potential for myotoxic effects. Hence, using a more hydrophilic agent is advisable in patients with preexisting muscle disease[6].

The primary treatment approach involves discontinuation of statins. However, it is prudent for clinicians to rule out other conditions causing myopathy and/or CK elevations, such as hypothyroidism, overt physical activity, and alcohol abuse. Clinically significant rhabdomyolysis requires hospitalization and intravenous hydration to prevent renal damage[6]. After resolution of muscle symptoms, clinicians have various options for treating dyslipidemia. This includes using a lower statin dose, switching to a different statin, or employing non-statin lipid-lowering agents. There might be an increased risk of myotoxicity with statin and fibrate combination therapy. Therefore, bile-acid resins may be the optimal choice for patients without triglyceride abnormalities who cannot tolerate statin therapy. While CoQ 10 supplementation has shown promise in reducing CK and aspartate aminotransferase level, there is also interest in the use of COQ 10, Chinese red rice yeast, and vitamin D for preventing or managing statin-associted myopathy, although the evidence is not definitive [6, 11, 12].

The treatment approach for statin-induced myopathy involves discontinuing statin use and closely monitoring patients clinically and through laboratory assessments for improvement. Rhabdomyolysis and renal failure may require adequate hydration and renal replacement therapies. It's crucial to distinguish between toxic statin myopathy and statin-induced autoimmune myopathy. Autoimmune statin myopathy is managed with interventions such as steroids, intravenous immunoglobulin, immunotherapy, plasmapheresis, alongside discontinuation of statins[8]. Distinguishing features between toxic statin myopathy and autoimmune statin myositis include early versus delayed presentation, a prevalence of 2%-20% versus two cases per million patients taking statins, CPK elevation of <10 times normal versus >10 times normal, improvement with statin discontinuation versus the need for additional treatments like steroids, immunosuppressants, and intravenous immunoglobulin in autoimmune cases, and the absence of muscle necrosis on biopsy versus the presence of muscle necrosis in autoimmune cases[8].

Rhabdomyolysis remains a challenging condition for both patients and healthcare providers. The distinct symptoms, including severe myalgia, urine discoloration, reduced urine output, acute renal failure, and other complications, leave a lasting impact on individuals who undergo this potentially life-threatening condition. Physicians face challenges in accurately diagnosing and treating this condition, particularly those directly involved in emergency care, outpatient clinics, inpatient settings, or dialysis units. Acute renal injury resulting from rhabdomyolysis is a well-established complication, often accompanied by hazardous metabolic and mineral imbalances. Hemodialysis is frequently necessary to address the renal insult and manage electrolyte abnormalities effectively.[12]

Conclusion

In this case, the suspected ADR was found to have a “probable” casual relationship with anti-tubercular therapy and severity belongs to the “moderate” category as per the Naranjo scale. To effectively prevent statin-induced rhabdomyolysis, it is crucial to address all risk factors. Specifically, individuals on statins engaging in intense physical activities, such as certain occupational workers and athletes, should integrate regular breaks to alleviate muscle strain and decrease the likelihood of rhabdomyolysis. Additionally, healthcare providers prescribing statins can prioritize the use of hydrophilic-type statins like pravastatin and rosuvastatin to minimize potential side effects. In summary, vigilant monitoring of statin usage is essential, with a specific emphasis on regularly assessing CK levels as an indicator of potential rhabdomyolysis. Patients should be educated about associated risks and warned about recognizable symptoms. Clinicians must conduct comprehensive screenings for risk factors and co-existing conditions, considering the potential future use of genotyping to enhance the safety of statin therapy. Initial management involves aggressive fluid therapy and addressing hyperkalemia. Subsequent lipid-lowering therapy following statin-induced rhabdomyolysis should be approached with caution.

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