Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Low-dose atorvastatin therapy induced rhabdomyolysis in a liver cirrhosis patient – a case report

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Introduction: Rhabdomyolysis may arise due to traumatic or non-traumatic causes leading to muscle injury. However, increased statin use has raised drug-related side effects like statin-related muscle damage.

Case report: A 74-year-old male with liver cirrhosis secondary to alcohol was prescribed atorvastatin for hyperlipidemia. He developed muscle tenderness and decreased muscle power 2 weeks following statin therapy, evident with a creatine phosphokinase level of more than 22 000 IU/l. The urinalysis also revealed positive for blood. Hence, atorvastatin was ceased. The patient's laboratory parameters improved significantly, implying atorvastatin is the causative agent for rhabdomyolysis.

Discussion: Statins are usually safe and well-tolerated drugs; however, skeletal muscle symptoms occur in ~5–10% of patients. The risk factor for statin-induced muscle injury includes advanced age, drug-altering statin plasma level, liver disease, or chronic kidney disease. Moreover, the hepatic level of CYP450 and its CYP3A4 isoform are altered in chronic liver diseases. CYP3A4 isoenzyme and its activity declines in hepatic cirrhosis patients.

Conclusion: Statins are generally prescribed for hyperlipidemia and primary and secondary prevention in high-risk cardiovascular diseases. However, several risk factors alter statin metabolism, causing statin-induced muscle injury. Thus, despite several studies suggesting otherwise, special precautions should be taken in patients with chronic liver disease.

Keywords: alcohol cirrhosis, atorvastatin, case report, liver cirrhosis, low-dose statin, rhabdomyolysis

Introduction

Rhabdomyolysis is a syndrome characterized by the release of intracellular muscle components, myoglobin, sarcoplasmic protein (creatine kinase, lactate dehydrogenase, aldolase, alanine, and aspartate aminotransferase), and electrolytes into the circulations after muscular injury[1]. Most cases arise due to traumatic or non-traumatic causes; however, the increased use of lipid-lowering drugs has increased the incidence of rhabdomyolysis from statins [3-hydroxy-3-methylglutaryl co-enzyme A(HMG Co-A)inhibitors]. Multiple pathophysiologic mechanisms contribute to statin-related muscle damage from myopathy, myalgia, myositis, and rhabdomyolysis[2]. This case report highlights rhabdomyolysis in low-dose atorvastatin therapy in a liver cirrhotic patient, a rare side effect who could tolerate the low-dose statin in the first episode of medication usage but developed a life-threatening complication in the subsequent prescription of atorvastatin.

HIGHLIGHTS

- Rhabdomyolysis is a release of intracellular muscle components in the circulation.
- Increased use of statins has increased the incidence of rhabdomyolysis.
- Adverse effects on skeletal muscles occur in ~5–10% of patients taking statins.
- The risk factors of statin-induced muscle symptoms include advanced age, drug-altering statin plasma levels, excessive physical activity, liver or chronic kidney diseases, and uncontrolled hypothyroidism.

Case presentation

A 74-year-old male with a medical history of hypertension, diabetes mellitus type 2, hyperlipidemia, and liver cirrhosis secondary to alcohol presented to the Emergency Department with chills, myalgia, and worsening aches in his joints for 3 days. He lived alone and had difficulty ambulating at home due to pain, especially in his ankle and elbow joints; hence, he presented to the Emergency. He had no chest pain, shortness of breath, fever, rash, abnormal body movements, sore throat, nausea, vomiting, diarrhea, and constipation. He reported initiation of low-dose atorvastatin therapy about 2 weeks ago, which was reintroduced after the gap of 3 years for hyperlipidemia. His medication included aspirin 81 mg once daily, hydrochlorothiazide 12.5 mg once

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2023) 85:5232–5234

Received 17 July 2023; Accepted 16 August 2023

Published online 1 September 2023

http://dx.doi.org/10.1097/MS9.0000000000001231

daily, losartan 12.5 mg once daily, metformin 500 mg once daily, atorvastatin 10 mg once daily, and propranolol 10 mg once daily. He had an 80-pack-year smoking history but ceased smoking about 3 months ago. He reported current alcohol use of 21.0 standard drinks per week. There was no history of any prescribed medications that alter the plasma concentration of statins or strenuous physical activity, causing rhabdomyolysis.

The patient was alert and oriented on examination, with a body mass index (BMI) of 26.7 kg/m^2. A physical examination revealed a blood pressure of 134/60 mmHg, a pulse rate of 77 beats/min, a respiratory rate of 18 breaths/min, a normal temperature, and an SPO_2 of 97% in room air. His abdomen was tense and non-tender, with normal bowel sounds. He had no fluid thrill nor ascites. The lungs were clear on auscultation, and the heart sounds were normal.

He had muscle tenderness with decreased muscle power in the lower extremity (1/5) bilaterally and extensor group in the upper extremity (1/5) bilaterally. His deep tendon reflexes, as well as sensory sensation in all limbs, and plantar reflexes (bilateral downward) were normal. The initial laboratory testing showed acute renal injury with increased serum creatine phosphokinase (CPK) levels in the blood and positive blood in urinalysis (Table 1).

He was admitted to the hospital with a diagnosis of rhabdomyolysis due to atorvastatin therapy. Hence, atorvastatin was stopped along with losartan and metformin. He was symptomatically managed with intravenous hydration and sodium bicarbonate therapy. Later, his general condition and laboratory parameters improved significantly with the cessation of atorvastatin, indicating the drug as the main culprit. Thus, he was discharged in good health.

Discussion

Statins have become a popular lipid-lowering drug in treating and managing dyslipidemias. This group of drugs mainly acts by targeting hepatocytes in the liver. It works by inhibiting the HMG-CoA reductase enzyme, primarily responsible for converting HMG-CoA into mevalonic acid; mevalonic acid serves as a cholesterol precursor[3]. Thus lowering lipid synthesis.

Numerous studies have demonstrated the role of statins in reducing mortality as well as morbidity in patients with high-risk cardiovascular disease[4]. Additionally, statins positively affect the primary and secondary prevention of liver cirrhosis. These statins alleviate oxidative stress injury, inhibit inflammatory cell activation, reduce inflammation reaction, and improve endothelial function through a nitric oxide-dependent pathway[5]. Some current studies indicate that statin usage in compensated liver cirrhosis patients is safe and may have favorable outcomes as it is inexpensive and well tolerated[6]. Hence, the patient was started on atorvastatin at a lower dose for dyslipidemia despite liver cirrhosis secondary to alcohol. However, the patient developed rhabdomyolysis, evident with muscle pain and a CPK level of more than 22 000 U/l.

Table 1

Laboratory investigation results.

	On admission	During hospitalization	On discharge
Hemoglobin, mg/dl	13.2	10.9	10.4
BUN, mg/dl	54	52	46
Creatinine, mg/dl	4	2.4	1.4
AST, mg/dl	1676	193	25
ALT, mg/dl	361	137	30
CPK, U/l	> 22 000	1791	200

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatine phosphokinase.

Although statins are usually safe and well tolerated, some side effects reported are myopathy and rhabdomyolysis; and less common are hepatotoxicity, peripheral neuropathy, impaired myocardial contractility, and autoimmune diseases[7]. The reported adverse effects on skeletal muscles occur in ~5–10% of patients taking statins[8]. Moreover, observational studies estimate that 10–15% of statin users develop statin-related muscular side effects, ranging from myalgia and fatigue to severe muscle symptoms with significant creatine kinase elevations[9]. Rhabdomyolysis is a particularly rare complication of statin monotherapy, with an incidence of 0.44 per 10 000 patient-years of exposure and a 1-year number needed to harm of 22 700 for atorvastatin[10].

According to the studies, mitochondrial dysfunction may be the important mechanism underlying statin myopathy associated with the reduction of CoQ10 levels. Other possible mechanisms could be reduced sarcolemmal cholesterol and isoprenoids in muscle fiber apoptosis[11]. Rhabdomyolysis may be higher in patients taking lovastatin, atorvastatin, and simvastatin because the CYP3A4 isoform of cytochrome P450 regulates their metabolism. Case fatality is ~10%[12]. Additionally, statins like rosuvastatin and fluvastatin had the lowest risk of myopathy.

Many studies revealed side effects of statins have been noted with the prescription of high doses of statins. Despite the initiation of the low-dose atorvastatin, the patient developed severe rhabdomyolysis within 2 weeks on the second episode of the drug usage after 2 years. The most important risk factors of statin-induced muscle symptoms are advanced age, female gender, drug-altering statin plasma levels, excessive physical activity, liver or chronic kidney diseases, uncontrolled hypothyroidism, metabolic syndrome, and vitamin D deficiency.

The cytochrome P450 (CYP) system is responsible for the metabolism of many drugs. Atorvastatin is mainly metabolized by CYP3A4, the important drug-metabolizing enzyme most abundantly found in the liver[13]. However, the hepatic level of CYP450 and its CYP3A4 isoform are altered in chronic liver diseases. CYP3A4 isoenzyme and its activity declines in hepatic cirrhosis patients. Hence, the liver's ability to eliminate many clinical therapeutic drugs and atorvastatin substrates declines subsequently[14]. This may lead to the manifestation of the adverse effects due to drugs. In this case, advanced age and liver cirrhosis might have a synergetic effect on developing rhabdomyolysis by atorvastatin due to decreased drug metabolism. Special consideration should be opted for by the practicing medical personnel while prescribing a statin to a patient with a risk of statin-induced muscle symptoms.

Conclusion

Statins are usually safe and well tolerated for hyperlipidemia and primary and secondary prevention of high-risk cardiovascular disease. However, several risk factors alter statin metabolism, causing statin-induced muscle injury. Among them, special precautions should be taken in patients with chronic liver disease despite several studies suggesting otherwise, as the hepatic level of

CYP450 and its CYP3A4 isoform are altered. This case report has been written in line with the SCARE 2020 criteria[15].

Ethical approval

According to the local ethical guideline, this case report does not constitute research according to Policy GF-IRB-322-009 of the Guthrie Clinic. We obtained written consent from the patient to include the clinical details.

Consent

Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

No funding was available for this research.

Author contribution

S.R.P. and Shraddha B.: reviewed the literature and designed the manuscript; Shashank B.: established the diagnosis, coordinated the patient's management with hospitalist and nephrologists, and treated the patient. All authors read and approved the final version of the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

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Data availability statement

Publicly available.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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