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Case Report

Rhabdomyolysis due to warfarin and atorvastatin combination therapy in a patient with ischemic heart disease: (A drug interaction)

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ABSTRACT

Introduction: Although atorvastatin has serious adverse effects, including hepatotoxicity and myopathy, it can cause drug interactions and side effects such as rhabdomyolysis and acute kidney injury, especially when combined with warfarin, which uses the same enzyme pathway for metabolism.
Case presentation: We describe a 66-year-old man with a history of ischemic heart disease who developed renal complications and rhabdomyolysis after concomitant use of atorvastatin and warfarin.
Discussion: Statins reduce serum LDL cholesterol levels significantly. It is a safe and cost-effective medicine used in the treatment of DLP as well as the primary and secondary prevention of CAD, atherosclerosis, myocardial infarction, and stroke. Despite their benefits, statins can cause side effects in various organs of the body, including the gastrointestinal tract, CNS, liver, and kidneys.
Conclusion: Statins are widely prescribed to patients with cardiovascular problems. Therefore, clinicians should pay attention to the patient's medical history, current prescribed doses, and drug interactions when adding new drugs or adjusting existing drugs.

1. Introduction

Dyslipidemia (DLP) is defined as a heterogeneous group of plasma lipoproteins and lipid abnormalities that affect the quality of life of millions of people all over the world. DLP is classified as either primary (genetic) or secondary (non-genetic). Primary DLP manifests in early childhood, but secondary DLP manifests in adulthood and is associated with a variety of illnesses, including atherosclerosis and obesity. In individuals with metabolic syndrome or diabetes, DLP is much too common. The most significant abnormalities are an increase in plasma low-density lipoprotein (LDL), hypertriglyceridemia, and a decrease in high-density lipoprotein (HDL) [1,2]. According to WHO studies, DLP is a known risk factor for ischemic heart disease (IHD), atherosclerotic cardiovascular disease (ACD), and cerebrovascular accidents (CVA). DLP was shown to be responsible for 40% of strokes, 60% of IHD events, and 56.9 million deaths worldwide in 2016 [3,4].

Statins are a class of medications that inhibit the enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase, reducing triglyceride and total cholesterol levels by decreasing LDL and elevating HDL levels. This class of drugs is known for being safe, with few side effects, and for cautious usage in patients and for prophylaxis [5,6].

Statins are used for DLP, primary and secondary prevention of coronary artery disease (CAD), atherosclerosis treatment, myocardial infarction, and stroke prevention alone or in combination with other methods such as diet and exercise. As a result, patients who should consume statins are frequently exposed to other drug classes used to treat cardiovascular disorders, such as anticoagulants and antiarrhythmics [7]. Herein, we report a rhabdomyolysis complication due to warfarin and atorvastatin combination therapy in a patient suffering from ischemic heart disease and dyslipidemia.

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2. Case presentation

On July 18, 2021, a 66-year-old man presented to the emergency department with complaints of tea-colored urine, lethargy, and weakness, as well as a malaise that began two days prior. He did not say anything about chest pain, costovertebral angle pain, dyspnea, or palpitation. The patient visited his cardiologist a week before admission and was diagnosed with atrial fibrillation, for which he was prescribed warfarin. Ischemic heart disease (IHD), hypertension (HTN), and DLP were all present in his medical history. Aspirin tablets (80 mg daily), propranolol tablets (20 mg daily), amlodipine tablets (10 mg daily), and atorvastatin were among the patient's routine drugs (80 mg daily). On initial examination, his blood pressure (BP) was 140/95 mm Hg and his heart rate (HR) was 76 beats/minute. His hemodynamic state was stable, with the exception of generalized muscle pain and weakness.

Laboratory tests revealed increased serum creatinine (Cr) at 5.8 mg/dL (reference range 0.6–1.3) and blood urea nitrogen (BUN), indicating acute kidney injury (AKI). A renal biopsy was performed, and the results demonstrated acute tubular necrosis with significant myoglobin-related cast formation. Rhabdomyolysis was diagnosed as a result of a drug interaction between warfarin and atorvastatin. During the hospitalizations, the patient received intravenous hydration as the first step in treatment, atorvastatin was stopped, and urine output was assessed.

The patient was admitted to the intensive care unit (ICU) for seven days, but after his BUN and serum creatinine levels decreased, he was transferred to the medical ward and discharged from the hospital after seven days. After three months, BUN and serum creatinine levels had returned to normal, and BP and electrolytes had also returned to normal. Written informed consent was obtained from the patient for the publication of this case report. This study was conducted according to the Declaration of Helsinki Principles. Also, CARE guidelines and methodology were followed in this study. The work has been reported in line with the SCARE 2020 criteria [8]. The study is registered with the research registry, and the UIN is research registry 7526 https://www.researchregistry.com/registernow#home/registrationdetails/61dc088913348d001fb2754c/

3. Discussion

Rhabdomyolysis is a life-threatening disease that begins with myalgia and progresses to myocyte necrosis, hyperkalemia, and the release of myoglobin into the bloodstream, which can damage the kidneys in a variety of ways, including mechanical obstruction of tubules due to precipitation in the glomerular filtrate, direct renal toxic effect of myoglobin, and hypovolemia [9].

As we know, statins reduce serum LDL cholesterol levels significantly [10]. It is a safe and cost-effective medicine used in the treatment of DLP as well as the primary and secondary prevention of CAD, atherosclerosis, myocardial infarction, and stroke.

Despite their benefits, statins can cause side effects such as dyspepsia, headaches, myalgia, gastrointestinal, central nervous system (CNS), and sleep problems, as well as hepatotoxicity and myopathies, which occur in less than 0.1–0.5% of patients. The event that may lead to rhabdomyolysis after simultaneous use with other drugs by the same enzymes and changing plasma concentration is dose-dependent on statin-induced myopathy. This dangerous condition occurs at a rate of 0.04–0.2% of the time [11–13].

Myoglobinuria and secondary AKI occur in approximately 10–40% of the population due to muscle biomarker secretion (creatine kinase) [11,12]. If no action is taken, this interaction could have disastrous consequences. It is recommended that the patient be closely monitored for skeletal muscle abnormalities and laboratory findings when on combined therapy with CYP inhibitors [11].

This patient's clinical symptoms have changed unexpectedly, requiring prompt referral, accurate monitoring, and sufficient support for findings from blood and urine analysis. The practitioner should weigh the benefits and hazards of statin use, as well as the potential for adverse effects, particularly when combined with other medications. In addition, they inform their patients about adverse events and perform timely investigations [13].

Our patient went to the hospital with fatigue, muscle weakness, malaise, and an increased serum creatinine level, as well as a history of using atorvastatin.

The co-administration of statins with other medications can increase the severity of this illness by up to tenfold. Warfarin inhibits the statin metabolic process competitively, hence increasing the pharmacological action of statins in muscle tissue and potentially increasing the risk of drug toxicity and rhabdomyolysis [14]. One week before the onset of his clinical symptoms, this patient was administered warfarin for atrial fibrillation. Combination therapy with these two medications, on the other hand, may result in an increase in INR after 4 weeks or bleeding through the same mechanism. As a result, INR monitoring is suggested [15].

It's because of drug-drug interactions (DDIs), which occur when one drug's effect is altered by another. Statins are the most commonly used medications in the treatment of cardiovascular underlying disease, either as monotherapy or in combination with other drugs such as warfarin as vitamin K antagonists (VKA). Warfarin is a routinely administered anticoagulant for thromboembolic therapy; nevertheless, due to its narrow therapeutic index, individual dosage responses, and drug interactions, it is sensitive to dose change [15,16]. Statins and warfarin have similar metabolic patterns, with both being metabolized by cytochrome P450 (CYP) enzymes in the liver, mainly CYP2C9 and CYP3A4 [15,17].

4. Conclusion

Statins are widely prescribed for patients, especially those with cardiovascular risk factors and the elderly. Therefore, clinicians should pay attention to the patient's medical history, current prescribed doses, and drug interactions when adding new drugs or adjusting existing drugs. The patient should be closely observed at all times, and any unexpected symptoms should be investigated further.

Provenance and peer review

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Ethical approval

The study was approved by our local ethics committee.

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None.

Author contribution

SKS and KR were involved in the interpretation and collecting of data and editing of the manuscript. ZZ and PKA involved in writing, editing, and preparing the final version of the manuscript. MS and are responsible for submitting the manuscript. All authors reviewed the paper and approved the final version of the manuscript.

Registration of research studies

https://www.researchregistry.com/register-now#home/registrationdetails/61dc088913348d001fb2754c/

Consent

Written informed consent was obtained from the patient for

publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Guarantor

Parastoo Karimi Aliabadi.

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References

[1] N. Patni, Z. Ahmad, D.P. Wilson, Genetics and dyslipidemia, in: K.R. Feingold, B. Anawalt, A. Boyce, G. Chrousos, W.W. de Herder, K. Dhatariya, et al. (Eds.), Endotext. South Dcartmouth (MA): MDText.Com, Inc.Copyright © 2000-2021, MDText.com, Inc., 2000.
[2] N. Pappan, A. Rehman, Dyslipidemia. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC., 2021.
[3] A. Pirillo, M. Casula, E. Olmastroni, et al., Global epidemiology of dyslipidaemias, Nat. Rev. Cardiol. (2021) 1–12.
[4] G.J. Mancini, R.A. Hegele, L.A. Leiter, Dyslipidemia, Can. J. Diabetes 42 (2018) S178–S185.
[5] O. Sizar, S. Khare, R.T. Jamil, R. Talati, Statin medications. StatPearls, in: Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC., 2021.
[6] W.D. Maxwell, L.B. Ramsey, S.G. Johnson, et al., Impact of pharmacogenetics on efficacy and safety of statin therapy for dyslipidemia, Pharmacotherapy 37 (9) (2017) 1172–1190.
[7] E. Streja, D.A. Streja, Management of Dyslipidemia in the Elderly, 2020. Endotext [Internet].
[8] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus surgical CAse REport (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230.
[9] I. Damiani, A. Corsini, S. Bellosta, Potential statin drug interactions in elderly patients: a review, Expet Opin. Drug Metabol. Toxicol. 16 (12) (2020) 1133–1145.
[10] S. Li, Y. Yu, Z. Jin, et al., Prediction of pharmacokinetic drug-drug interactions causing atorvastatin-induced rhabdomyolysis using physiologically based pharmacokinetic modelling, Biomed. Pharmacother. 119 (2019), 109416.
[11] P. Esposito, L. Estienne, N. Serpieri, et al., Rhabdomyolysis-associated acute kidney injury, Am. J. Kidney Dis. 71 (6) (2018) A12–A14.
[12] T. Petreski, N. Piko, T. Petrijan, et al., Statin-associated necrotizing myopathy leading to acute kidney injury: a case report, Case Rep. Nephrol. Dialysis 11 (2) (2021) 129–135.
[13] M.F.H. Mohamed, O.K. Salameh, A.A.M. Saeed, Statin-induced rhabdomyolysis, acute kidney injury, and hepatitis leading to death, Am. J. Case Rep. 20 (2019) 709–712.
[14] J.W. Mackay, M.E. Fenech, K.S. Myint, Acute rhabdomyolysis caused by combination therapy with atorvastatin and warfarin, Br. J. Hosp. Med. 73 (2) (2012) 106–107.
[15] A.E. Engell, A.L.O. Svendsen, B.S. Lind, et al., Drug-drug interactions between vitamin K antagonists and statins: a systematic review, Eur. J. Clin. Pharmacol. 77 (10) (2021) 1435–1441.
[16] A.N. Shaik, T. Bohnert, D.A. Williams, et al., Mechanism of drug-drug interactions between warfarin and statins, J. Pharmaceut. Sci. 105 (6) (2016) 1976–1986.
[17] A.E. Engell, A.L. Svendsen, B.S. Lind, et al., Drug-drug interaction between warfarin and statins: a Danish cohort study, Br. J. Clin. Pharmacol. 87 (2) (2021) 694–699.