Journal of Preventive Epidemiology

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High dose statin-associated myopathy, rhabdomyolysis and acute kidney injury in Asian ethnic population

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Received: 5 June 2015
Accepted: 19 July 2016
ePublished: 14 Aug. 2016

Keywords: Acute kidney injury, Myopathy, Myotoxicity, Rhabdomyolysis, Statins

Citation: Vikrant S, Gupta D. High dose statin-associated myopathy, rhabdomyolysis and acute kidney injury in Asian ethnic population. J Prev Epidemiol. 2016;1(2):e13.

Abstract

Statins are considered to be safe, well tolerated. Severe myopathy and rhabdomyolysis is the most intense adverse effect of statins, which may result in acute kidney injury (AKI), disseminated intravascular coagulation and death. According to recent guidelines treatment with high-intensity statins is recommended for primary or secondary prevention of cardiovascular disease. This is a report of three Asian ethnic patients who developed severe myopathy, rhabdomyolysis and AKI due to treatment with high-intensity statin therapy. Though, high-potency statins are more effective in improving cardiovascular outcomes, but there is increased the risk of AKI with their use. Asian experience blood levels of the drug twice as high as non-Asians. This higher blood level could predispose to severe myopathy. Further, there is high prevalence of vitamin D deficiency in this population which synergistically interacts with statins to cause myotoxicity. Unfortunately, the data on the long term safety and efficacy of high dose statin therapy in Asian ethnic population is lacking. These cases highlight the risk of high-intensity statin and make a case for moderate-intensity statin and correction of hypovitaminosis D before instituting statin therapy in Asian ethnic population.

Introduction

Statins are considered to be safe, well tolerated and the most efficient drugs for the treatment of hypercholesterolemia, one of the main risk factor for atherosclerosis, and therefore they are frequently prescribed medications (1). The most severe adverse effect of statins is myotoxicity, which manifests in the form of myopathy, myalgia, myositis or rhabdomyolysis. The myotoxicity, defined as myalgia or muscle weakness with creatine kinase (CK) levels greater than 10 times the normal upper limit, is a well known complication of statin therapy Rhabdomyolysis is the most severe adverse effect of statins, which may result in AKI, disseminated intravascular coagulation and death (2,3).

According to recent guidelines treatment with high-intensity statins is recommended in adults for primary or secondary prevention of cardiovascular disease (4,5). Use of high-potency statins (≥10 mg rosuvastatin, ≥20 mg atorvastatin, ≥40 mg simvastatin) has been shown to be more effective in improving cardiovascular outcomes than use of lower-potency statins. However, the high-potency statin therapy may increase the risk of acute kidney injury (AKI) (6). This is a report of three Asian ethnic patients who developed severe myopathy, rhabdomyolysis and AKI due to treatment with high-intensity statin therapy and reviews the implications of this complication in light of recent guidelines on cholesterol management.

Core tip

High-intensity statins are recommended for primary or secondary prevention of cardiovascular disease. Data on safety and efficacy of this strategy in Asian ethnic population is lacking. This case series describes three Asian ethnic patients who developed severe myopathy, rhabdomyolysis and acute kidney injury (AKI) due to treatment with high-intensity statin therapy. These cases highlight the risk of high-intensity statins and make a case for a strategy of moderate-intensity statins in Asian ethnic population

Case 1

A 77-year-old Asian ethnic man with hypertension, stroke was hospitalized with acute coronary event in the form of ST elevated myocardial infarction. Statins in form 40 mg of atorvastatin was added to his medications. Three weeks later he was readmitted with generalized weakness. He had proximal limb weakness and difficulty in chewing and swallowing food. The serum CK level was in-

creased at 6772 IU/L and serum creatinine level on admission was 2.8 mg/dL. Urinalysis showed cola-colored urine without red blood cells. Atorvastatin therapy was stopped and an aggressive regimen of intravenous fluids was implemented, along with urinary alkalinization. Kidney function subsequently improved without the need for renal replacement therapy and normalized after two weeks.

Case 2

A 58-year-old Asian ethnic man with hypertension and ischemic heart disease was admitted with two weeks history of generalized bodyaches and muscle pain. He also had complaints of malaise, anorexia and vomiting. His medications included atorvastatin 20 mg for past four months. Urine myoglobin was positive at 113 µg/L and CK level was grossly increased at 8800 IU/L.

Atorvastatin therapy was stopped and the CK level decreased to normal values in a week. Serum creatinine level on admission was 10.6 mg/dL and the patient was subjected to four sessions of hemodialysis. The patient had a normal electromyogram which excluded inflammatory myopathy. Kidney biopsy showed features of features of acute tubular injury with interstitial edema and patchy acute interstitial nephritis. There was gradual improvement in kidney functions and serum creatinine improved to 1.1 mg/dL on follow up visit at 7 weeks.

Case 3

A 46-year-old Asian ethnic man was diagnosed coronary artery disease and was found to have double vessel disease for which he had undergone percutaneous angioplasty 8 months back. He developed the complaints of weakness, muscle pain and difficulty in walking for about a week. He was found to have rhabdomyolysis with CK level grossly increased at 8704 IU/L and AKI with serum creatinine of 2.2 mg/dl. His medications included rosuvstatin 40 mg, which was discontinued. He was treated with aggressive hydration with IV fluids and urine alkalinization. He improved and the levels of CK and creatinine had normalized at 3 weeks. He was found to have severe vitamin D deficiency (<10 ng/mL).

Discussion

Known risk factors for the development of statin-associated myopathy include a history of muscle symptoms or elevated CK, hypothyroidism, female sex, older age, renal and hepatic insufficiency, diabetes, excessive alcohol consumption, and concomitant use of medications that increase the serum concentration of statins (2,3). Asian experience blood levels of the drug twice as high as non-Asians. This higher blood level could predispose to severe myopathy (2).

According to the 2013 guidelines of the American College of Cardiology and the American Heart Association (ACC–AHA) for the management of cholesterol, a high-intensity statin therapy is recommended in individuals who have clinical atherosclerotic cardiovascular disease (ASCVD), diabetes with the low-density lipoprotein (LDL) cholesterol level ≥70 mg/dL, LDL cholesterol ≥190 mg/dL, and those with 7.5% or higher 10-yearis risk estimate of cardiovascular disease (4). These new ACC–AHA guidelines for the treatment of cholesterol expand the indications for statin therapy would increase the number of adults who would be eligible for statin therapy (7). The lipid modification guidelines of 2014 by the National Institute for Health and Care Excellence (NICE), United Kingdom and the 2013 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on the management of lipid levels in chronic kidney disease (CKD) are more inclusive (5,8). Unlike the ACC–AHA guidelines, which include a lower limit for the LDL cholesterol level (70 mg/dL) and an upper limit for age (75 years), the NICE and KDIGO guidelines do not include these limits. The NICE and KDIGO guidelines, as compared with the ACC–AHA guidelines, may further increase the eligibility of older patients, since the prevalence of CKD is high among those with age ≥ 75 years.

Although, a large number of future cardiovascular events may be prevented by implementation of these new guidelines, concern should be raised about the well-established side effects of the statin therapy. It is predicted that the implementation of the new ACC–AHA guidelines would be associated with a large increase in new cases of severe myositis and rhabdomyolysis (9). This would generate a remarkable clinical and economic burden that should be accurately weighted before recommending widespread implementation of these guidelines. There is likely to be considerable interest in prospectively testing of these guidelines in multiple groups of various ethnic backgrounds.

The incidence of statin-induced myopathy is considerably lower in randomized controlled trials of statin efficacy than in observational studies of real-world patients because these trials excluded patients at risk of toxicity. In observational studies of unselected patients, muscle symptoms occurred in up to 20% of patients (10).

Asian ethnic population has characteristics predisposition to statin-associated adverse effects (2). A high prevalence of hypovitaminosis D has been witnessed in South Asian countries (11). Low serum vitamin D can cause myalgia, myositis, myopathy, and myonecrosis. Low vitamin D additively or synergistically interacts with statins to cause myalgia-myopathy. Low serum vitamin D level is associated with statin intolerance. Statin-induced myalgia in vitamin D deficient patients can often be resolved by vitamin D supplementation, normalizing serum vitamin D levels (12). High prevalence of vitamin D deficiency may increase the risk of statin myotoxicity in Asian ethnic population. Therefore, vitamin D levels should be measured and hypovitminosis D should be corrected before instituting statin therapy.

Unfortunately, the data on the long term safety and efficacy of high dose statin therapy in Asian ethnic population is lacking. In some Asian countries, doses of statins tend to be lower than those used in Western countries, due to concern about drug toxicity and clinical trial data indicating that such doses safely reduce LDL-C and improve clinical

outcomes (13). The three cases reported herein had clinical ASCVD and they suffered the complication of serious myopathy, rhabdomyolysis and AKI due to treatment with high dose statin. These cases highlight the risk of high-intensity statin and make a case for moderate-intensity statin if high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present. One has be alert and avoid nephrotoxic medications or interventions in patients on high dose statin therapy. A moderate-intensity statin therapy (atorvastatin, 10 to 20 mg; rosuvastatin, 5 to 10 mg; simvastatin, 20 to 40 mg) may be a safe and practical option in Asian ethnic population till high dose statins are tested in this population and safety data on their use emerges.

Measurements of serum CK should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate decision of whether to continue therapy or alter doses.

Statins are discontinued and intravenous hydration therapy in a hospital should be instituted if indicated for patients experiencing rhabdomyolysis. Once patients recover, risk versus benefit of statin therapy should be carefully reconsidered.

Conclusion

Although recent guidelines recommend high dose stains to improve cardiovascular outcomes, but there is increased the risk of severe myopathy, rhabdomyolysis and AKI with their use in Asian. Higher blood level of stains and high prevalence of vitamin D deficiency predisposes to increased risk of myotoxicity. A strategy of a moderate-intensity statins and correction of hypovitaminosis D before instituting statin therapy should be adopted in Asian ethnic population.

Authors' contribution

SV conceived the study and wrote the manuscript. DG reviewed the manuscript. All authors read and sign the final manuscript.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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