Rhabdomyolysis induced by co-administration of fluvastatin and colchicine

Rabdomiolisi indotta da somministrazione contemporanea di fluvastatina e colchicina

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ABSTRACT: Rhabdomyolysis induced by co-administration of fluvastatin and colchicine. F.M. Sarullo, L. Americo, A. Di Franco, P. Di Pasquale.

A case of fluvastatin-induced rhabdomyolysis after co-administration of colchicine is reported. A 77 year old man with ischemic heart disease, chronic pericardial effusion, diabetes mellitus, dyslipidemia, arterial hypertension, chronic renal failure (stage 2 of classification of chronic kidney disease of National Kidney Foundation) and chronic gout presented with a generalized muscle pain. The patient had been taking 80 mg/day of fluvastatin for 4 years, and, for four weeks before presentation, he had also been taking a dose of colchicine (1.0 mg daily) for an exacerbation of gout. Investigations confirmed the diagnosis of rhabdomyolysis. Discontinuation of fluvastatin and colchicine therapy and adequate fluid administration resulted in the resolution of clinical and biochemical features of rhabdomyolysis.

Although neuromuscular adverse effects of fluvastatin and colchicine are well recognized, rhabdomyolysis is rare, making this is only the second case reported of fluvastatin and colchicine co-administration induced rhabdomyolysis in literature.

Keywords: rhabdomyolysis, colchicine, fluvastatin.

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Introduction

Rhabdomyolysis is a clinical and biochemical syndrome resulting from skeletal muscle injury and the release of muscle cell constituents into the circulation. It may result in myoglobinuria, the filtration of myoglobin into the urine, and it is often associated with acute renal failure (1). Drug-induced rhabdomyolysis occurs rarely and may be asymptomatic. However, life-threatening severe electrolyte disorders and acute renal failure may occur in more serious cases (2). Rhabdomyolysis is the results of an inherited muscle enzyme deficiency, toxins such as alcohol abuse and cocaine, trauma, drugs such as statins, muscle overexertion, infections, and other disorders (3). Colchicine is a unique anti-inflammatory agent that has been therapeutically used in acute gout for over 230 years. The adverse effects of the drug range from nausea, vomiting, diarrhea, and abdominal pain to agranulocytosis, aplastic anemia, and alopecia (4). Colchicine has been reported to cause myoneuropathy (5) and myotonia (6) especially in presence of renal impairment. However, rhabdomyolysis induced by colchicine is rare (7,8). Rhabdomyolysis with the use of statin-colchicine combinations has been reported only in one case (9). Here, we report to our knowledge the second case in literature of a patient who developed rhabdomyolysis after that colchicine was added to statin (fluvastatin) therapy.

Case report

A 77 year old man was admitted to our hospital with complaints of myalgia, nausea, vomiting, and muscle weakness for the last few days. His medical history revealed that percutaneous coronary intervention (PCI) plus drug eluting stent (DES) on left descending coronary artery (LAD) was performed for treatment of critical coronary stenosis 4 years prior. Moreover, he had suffered from chronic pericardial effusion for two years, diabetes mellitus and dyslipidemia for twelve years, arterial hypertension for twenty-five years, chronic renal failure [stage 2 of classification of chronic kidney disease of National Kidney Foundation (10)] for five years and chronic gout for four years. He had used aspirin, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, nitrates, calcium antagonists, furosemide, insulin and 80 mg a day of fluvastatin for the treatment of coronary artery disease for 4 years. For four weeks before the presentation, he also had been taking colchicine 1.0 mg daily for acute gouty arthritis. Fourteen days after initiation of colchicine therapy, the patient started reporting stomach ache and nausea. He later developed increasingly severe pain in
his arms and legs as well as weakness. On admission, axillary temperature was 36.4°C, blood pressure 150/90 mmHg, and heart rate 70 beats/min, body mass index (BMI) 28.6 Kg/m². The patient had a jaundiced skin colour. Thoraco-abdominal examination was unremarkable. There was no rash or lymphadenopathy. Neurologic examination presented diffuse muscle tenderness and muscle weakness. Relaxation of deep-tendon reflexes were grossly delayed. Electromyography revealed polyphasic action potentials consistent with myopathy. The routine electrocardiogram displayed a pacemaker rhythm. The routine laboratory tests revealed an increased creatine kinase (CK) level to 2371 U/L (normal range 25 to 195 U/L), with a MB isoenzyme of 27.42 ng/ml (normal range 0.10 to 5.0 ng/ml), a myoglobin level > 3000 ng/ml (normal range 0 to 85 ng/ml). Furthermore, laboratory results showed haemoglobin (Hb) 11.9 gr/dl (normal range 12 to 18 gr/dl), white blood cell count 5.830/mm³, and platelet count 163.000/mm³. Fasting blood glucose was 98 mg/dl, BUN 68 mg/dl, serum creatinine 1.74 mg/dl, clearance creatinine according to MDRD formula 40.6 ml/min/1.73 m², albumin 4.9 gr/dl, serum potassium 4.7 mEq/l, serum sodium 127 mEq/l, calcium 9.9 mg/dl, phosphorus 7.4 mg/dl aspartate aminotransferase (AST) 617 IU/l, alanine aminotransferase (ALT) 523 IU/l, lactate dehydrogenase (LDH) 785 IU/l, total bilirubin 4.0 mg/dl and indirect bilirubin 3.9 mg/dl. Urinalysis showed 0.456 gr/dl proteinuria thus, no erythrocyte or cast. Auto-antibodies such as antinuclear antibody (ANA), anti-dsDNA antibody, and anti-Jo-1 and the serologies for brucellosis, human immunodeficiency virus (HIV), and hepatitis B and C virus were negative. C3 and C4 complement level were normal. Thyroid function tests and anti-thyroid peroxidase (TPO) antibody titer were normal. There were no urinary obstruction findings. During the abdominal ultrasound the size of the liver and kidney were normal.

Fluvastatin and colchicine were discontinued. The patient was treated with a infusion of NaCl 0.9% and oral steroid was administered for acute gouty arthritis. As the patient’s urine output increased, serum creatine and CK decreased steadily. He was discharged 16 days after admission, feeling well, with CK 85 IU/l, and creatinine 1.34 mg/dl. Fluvastatin was reintiated after CK level was normalized. Six months later, he was free from symptoms.

Discussion

Statins drop low-density lipoprotein levels and serum total cholesterol and raised high-density lipoprotein levels. Statins are effective in both primary and secondary prevention of ischemic heart disease. As a group, these drugs are well tolerated with a low incidence of side effects. Myopathy occurs in 0.1% to 0.5% of patients (11).

Adverse effects of statins are frequently associated with drug interactions because of their long-term use in older patients who are likely to be exposed to polypharmacy. In the PRIMO study, 30% of patients that assumed a high-dose of statin therapy that developed muscle-related symptoms, iden-

148
Il paziente aveva assunto 80 mg/die di fluvastatina per 4 anni, e per quattro settimane prima della presentazione in ospedale, aveva anche assunto una dose di colchicina (1.0 mg al giorno) per una esacerbazione della gotta. Le indagini cliniche e strumentali suggerivano la diagnosi di rabdomiolisi. L’interruzione della terapia con fluvastatina e colchicina ed un’adeguata idratazione con fluidi per via parenterale, è valsa alla risoluzione della sintomatologia muscolare e del quadro laboratoristico.

Anche se gli effetti neuromuscolari negativi della fluvastatina e della colchicina sono ben noti, la rabdomiolisi è un evento molto raro. A nostra conoscenza questo è il secondo caso di rabdomiolisi determinato dalla co-somministrazione di fluvastatina e colchicina segnalato in letteratura.

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References