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CASE REPORT

Rhabdomyolysis induced by co-administration of fluvastatin and colchicine

Rabdomiolisi indotta da somministrazione contemporanea di fluvastatina e colchicina

Filippo M. Sarullo[1], Luigi Americo[1], Antonino Di Franco[1], Pietro Di Pasquale[2]

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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Division of Cardiology, Buccheri La Ferla - Fatebenefratelli Hospital, Palermo, Italy.
[2] Division of Cardiology "P. Borsellino", G.F. Ingrassia Hospital, Palermo, Italy.

Corresponding author: Filippo M. Sarullo MD; Division of Cardiology; Buccheri La Ferla Fatebenefratelli Hospital; Via Salvatore Puglisi n.15; 90143 Palermo, Italy; Phone: +39.091.479.263; Fax: +39.091. 342.336; E-mail address: fsarullo@neomedia.it

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 anaemia, 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 day 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 lymphoadenopathy. 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 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. Autoantibodies 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 peroxidise (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 reinitiated 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, identified the beginning of a new medication as a trigger (12). Drug interactions involving statins may have either a pharmacodynamic or pharmacokinesic basis, or both. Cytochrome P450 enzymes play an important part in the metabolism of statins, leading to clinically relevant interactions with other agents, particularly cyclosporin, erythromycin, itraconazole, ketoconazole, HIV protease inhibitors, and colchicine, that are also metabolized by this enzyme system. According to Atasoyu and co-workers (9), two different mechanisms may be responsible for the pathogenesis in our patient. Drug interactions that potentiate adverse effects may occur when colchicine is co-administered with fluvastatin since both drugs are metabolized by cytochrome P450 isoenzymes and myotoxic effects are well known (7-8). Fluvastatin and colchicine, however, are cleared through two different CYP450 isoenzymes. The second possible mechanism is synergistic myotoxicity (13). Pathogenesis of colchicine myopathy may be related to the disruption of a cytoskeletal microtubular network that interacts with lysosomes. In addition, fluvastatin therapy is associated with myonecrosis, membranous myeloid bodies, and vacuolization, and all this can disrupt cytoskeletal integrity. The combined use of these drugs may determine a synergistic drug-induced myopathy involving both pharmacokinetic and related pharmacodynamic mechanisms.

Our theory about the causes responsible for muscular side effects in our patient was the addition of colchicine to fluvastin 80 mg, taken for many years (5 years), without any symptom related to the statin treatment. Muscular symptoms appeared only after beginning colchicine treatment. Unfortunately, we began observing the patient only 4 weeks after the treatment with colchicine and due to this reason we were unable to control laboratory parameters before treatment. These data suggested that the side effects were related to the addition of colchicine.

In conclusion, this case highlights a rare but serious and potentially life threatening neuromuscular adverse effect of co-administration of fluvastatin and colchicine. Since pre-existent renal impairment is a predisposing factor for neuromuscular toxicity, cautious dosing of colchicine is warranted in the presence of abnormal baseline renal function.

Physicians should be aware of potentially lethal adverse effects including rhabdomyolysis and acute renal failure after colchicine added to statin therapy. Furthermore, they should carefully follow-up renal, hepatic, and muscle enzymes in all patients. Patients should also be informed about risks of the drugs and about symptoms of potential adverse effects of the drugs such as myalgia and muscle weakness.

Riassunto

Viene riportato il caso di un uomo di 77 anni affetto da cardiopatia ischemica cronica, diabete mellito tipo II, dislipidemia con pattern II B, ipertensione arteriosa, insufficienza renale cronica di grado lieve e gotta cronica, che veniva alla nostra osservazione per violenti dolori muscolari agli arti inferiori.

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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