Case Report

Rhabdomyolysis and acute kidney injury requiring dialysis after norfloxacin-rosuvastatin co-administration

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Abstract

Aims: The increasing use of electronic gadgets from medical students raises awareness for related health disorders such as visual complaints. A 67-year-old male presented at the Emergency Department, because of severe, gradually deteriorating weakness and muscle pain for the past fifteen days. He had been on norfloxacin for the last three weeks due to a recently diagnosed acute prostatitis. He was also receiving rosuvastatin as chronic treatment for dyslipidemia. Extended proximal muscle wasting was the only pathological finding after a thorough clinical examination, while the lab tests confirmed excessive acute rhabdomyolysis with consequent acute kidney injury, requiring hemodialysis. During hospitalization extensive work up was not able to establish any specific diagnosis for the underlying disease. The aforementioned incident was eventually attributed to the co-administration of norfloxacin and rosuvastatin. Discontinuation of both drugs resulted in gradual alleviation of the symptoms, supporting our clinical hypothesis. However, the patient underwent multiple hemodialysis sessions for three months, before finally restoring his previous kidney function.

Introduction

Statin-induced myopathy is a well-described side effect of statins, usually occurring with atorvastatin or simvastatin during the first few weeks of treatment or after increasing the administered dose.[1,2] Temporary withdrawal of the drug or dose reduction is highly advisable in those cases.[2] However, when a patient has been uneventfully taking a statin for a longer period and such an effect is suddenly presented, it is more than often correlated with other causes of myositis, or with a recent, concurrent use of another drug. Antifungals, macrolides, fibrates, and cyclosporine are known to interfere with the metabolism of statins in more than one possible way, thus leading to the accumulation of the drug, followed by an increase in statin-related adverse effects.[2-5] Although not commonly reported, fluoroquinolones may also have such effects, when co-administrated with statins.[6-8] Awareness of such interactions seems to be of great significance, since quinolones are often enough prescribed for common infections to outpatients. Therefore, they could provoke effects that could easily go unnoticed.

Case Presentation

A man in his late 60s presented to the hospital, due to severe weakness and pain in his lower extremities. The patient reported muscle weakness, which started almost two weeks ago, while his daily routine remained the same as always, with no excess in physical effort. He also stated that his weakness got worse in time and muscle pain was recently added to the symptoms. One week prior to the symptoms' onset, he was diagnosed with acute prostatitis and had started treatment with norfloxacin (400mg per tab). Patient's medical history included diabetes mellitus, ischemic heart disease, thrombocytopenia and anemia related to myelodysplastic syndrome, and dyslipidemia. Chronic medication included aspirin (100mg), vildagliptin/ metformin (50/850mg), bisoprolol (2.5 mg), ramipril (5mg) and rosuvastatin (40mg). He was an active swimmer, non-smoker, with no known allergies, and reported alcohol consumption only occasionally. Clinical examination revealed severe symmetrical, proximal muscle weakness and tenderness concerning bilateral shoulder girdle muscles, quadriceps, and hip muscles (muscle strength grading 3/5). The biceps, brachioradialis, and triceps reflexes were decreased, while the patellar and achilles reflexes were absent. No prominent signs of arthritis, skin rash, or indications of nerve damage were present.

Investigation. Routine laboratory tests revealed a significant elevation of creatine kinase levels (CPK 31000 U/l), an increase in the liver function enzymes (aspartate aminotransferase 1027 U/l - reference levels <37, alanine transferase 421 U/l - reference levels <41), as well as increased levels of blood urea nitrogen and creatinine (BUN 104 mg/dl, cre 7.5 mg/dl). Aerial blood gases were indicative of mild metabolic acidosis, as a result of the acute kidney injury. The kidney dysfunction was mainly attributed to the rhabdomyolysis and myoglobinuria, since clinical presentation, history, urinary analysis and kidney ultrasound excluded other causes such as hypoperfusion, glomerular disease, and urinary outflow obstruction.

Differential Diagnosis. The sudden onset and deterioration of symptoms are compatible with all forms of acquired myopathy. Hypomagnesemia and hypo- or hyperkalemia are some of the most prominent candidates for myopathy,9 but they were easily excluded as the cause. Infectious or endocrine disorders, such as HIV infection, Cushing's disease or thyroid abnormalities were also excluded. Autoimmune

and inflammatory myopathies are also included in the differential diagnosis; tests for myositis-specific autoantibodies (c-ANCA, p-ANCA, anti-PR3, anti-MPO) were negative, while serum aldolase levels were between normal limits.[10]

A myopathy mediated by anti-HMG-CoA reductase antibodies was another considerable possibility, but was rejected, since the patient had already improved in a few days after discontinuation of the norfloxacin and rosuvastatin, without any specific treatment.[11-14] Statin-induced myopathy incited by the recently co-administered fluoroquinolone was the most prevalent scenario for this clinical case, as an exclusion diagnosis.

Treatment, Outcome and Follow-up. Intravenous crystalloid fluids were administered, in order to ameliorate the kidney injury. During hospitalization and a few days after the discontinuation of norfloxacin and rosuvastatin, the creatine kinase levels gradually became normal and the patient regained his physical strength. Liver function enzymes also improved. However, the patient remained hospitalized due to persistent oliguric kidney injury and dysfunction, since the serum creatinine levels deteriorated, before finally reaching a plateau in four to six days. *(Figure 1)*

Because of the oliguria and persistent metabolic acidosis despite the administration of sodium bicarbonate intravenously, the patient entered into hemodialysis sessions.

After being successfully mobilized, he was discharged from the hospital and continued hemodialysis sessions in an outpatient facility. Three months later, his kidney function was finally getting back to normal and he had also returned to his daily activities without any restrictions. At the time, he was still on most of his chronic medication with the exception of rosuvastatin. Almost five months after hospitalization he started treatment with atorvastatin (20mg per day), while he continued receiving the rest of his chronic medication with no modifications.

At a follow-up of one year, he is free of symptoms with normal physical activity and normal laboratory test evaluation.

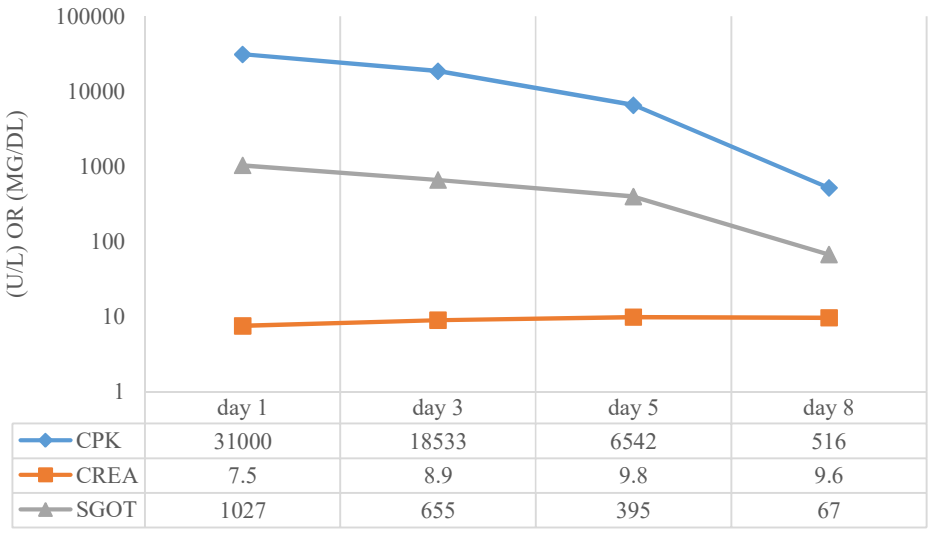

Figure 1. Variation in creatine kinase [CPK], serum creatinine, and aspartate aminotransferase [SGOT] levels during our patient's hospitalization.

Discussion

Statins are considered the cornerstone of drug therapy for dyslipidemia, while they are also crucial in the primary and secondary prevention of cardiovascular events.[15] The lipid-lowering mechanism of statins is well known; they act as HMG-CoA reductase inhibitors, thus limiting cholesterol synthesis in the liver.[16] On the other hand, the mechanism of statin-induced myopathy is vague and indefinite. It has been proposed that the reduction in the cholesterol levels, which statins provoke, may have a negative impact on the myocyte cell membrane stabilization, as well as on mitochondrial activity, not only disrupting the function of the muscle cell but also making it more prone to apoptosis.[1-4] In addition, it was postulated that the lipophilicity of the drug might play a crucial role in muscle cell damage, since lipophilic statins may permeate the cell membrane, reach the cytoplasm and instigate

myotoxicity more easily when compared to hydrophilic agents (e.g. rosuvastatin).[1-4] The aforesaid theory, however, seems to be rejected by some meta-analyses.[17] Most studies implicate a link between the likelihood of statin-related myotoxicity and co-prescribed drugs, which interfere with statin metabolism.[2-4] Several similar case reports shed light on the possible mechanisms of the interaction between statins and fluoroquinolones;[6-8] the current theories usually pertain to the inhibition of the CYP metabolic pathway by quinolones.[8,18] Any restriction of CYP activity leads to the accumulation and toxic levels of CYP substrates, such as statins.

In our case, the most possible scenario was that norfloxacin slowed down or even blocked the metabolism of rosuvastatin, which is primarily metabolized to N-desmethylrosuvastatin by CYP2C9; nevertheless, norfloxacin is not a common inhibitor of CYP2C9.[19,20] Moreover, according to on-topic studies, it is unlikely that either stimulation or inhibition of the said metabolic pathway could provoke effects of such clinical severity.[21,22,23] Pharmacogenetics may be the key to why our patient had such an extreme response to the co-administration of these two drugs.[2,4,22]

Conclusion

Statins are commonly prescribed drugs and statin-associated myopathy is a well-described medical condition. Physicians should be aware of this side effect. Co-administration of statins and other medicine seems to enhance the likelihood of developing myopathy, via inhibition of the statins' CYP-mediated metabolism. The severity of symptoms may vary from mild myalgias to significant rhabdomyolysis. Patients prescribed statins should be informed by their physician about the possible side effects of the drug, in order to seek medical assistance immediately if need be.

Conflict of Interest

The authors declare no conflict of interest.

Patient Consent Form

Written consent form obtained

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