CASE REPORT

Co-prescription of ciprofloxacin and statins; a dangerous combination: Case report

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Abstract

Drug interaction is a common clinical problem which is often underestimated by physicians. Statins are one of the commonly prescribed medicines worldwide that are generally well tolerated. Muscle-related symptoms have a varied clinical presentation which usually increases if a new medicine is co-prescribed. We report the case of a 65-year-old woman who presented with a 10-day history of extreme fatigue, slowly progressing muscle weakness and insomnia. Drug-induced myopathy was diagnosed with concomitant use of atorvastatin and ciprofloxacin. Muscle weakness improved after the medicines were withdrawn. Co-prescription of Ciprofloxacin and statin therapy appeared to have contributed to muscle weakness in this patient. Drug interaction should also be kept in mind, when managing patients on statins as it may be underappreciated as a cause of muscle weakness and its consequences can have potentially serious outcomes.

Keywords: Atorvastatin, Ciprofloxacin, drug interaction, myopathy.

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Introduction

Drug interaction is a common clinical problem which is often underestimated by physicians. It is of primary concern, especially in older patients, as the likelihood of experiencing a drug interaction increases with polypharmacy.

With substantial increase in non-communicable diseases, the use of statin has increased dramatically over the last few decades. Overall, it has increased by almost 79% among adult population in both the developed and developing countries.[1] Statins are generally considered safe and well tolerated, but an important concern is the potential risk of adverse muscular problems;[2] which is further increased with co-administration of a new medicine. These adverse effects can range from mild transient muscle pain (5%) or weakness (0.1%) without elevation of creatinine kinase levels, to serious myopathy with elevation of creatinine kinase levels that may progress to rhabdomyolysis (0.01%) and, occasionally, death.[3]

This is perhaps one of the rare reported cases of myopathy caused due to interaction of atorvastatin and ciprofloxacin. We describe, herein, a case of reversible drug-drug interaction that showed remarkable improvement with timely management.

Case Report

A 65-year-old woman, initially seen at a private hospital in Al-Ahssa in Saudi Arabia for urinary complains, was started on ciprofloxacin. She developed extreme fatigue, progressing muscle weakness, agitation and insomnia. As her condition worsened, the patient and the family privately consulted a general practitioner (Family Medicine consultant) for advice in May 2018. Her medical history was significant for coronary artery disease and Atorvastatin 80mg/day, Bisoprolol 5mg twice daily, aspirin 81mg/day, Ticagrelor 90mg twice daily, Perindopril 5mg daily had been prescribed by her cardiologist.

The patient presented with a short history of diffuse muscle pain and bilateral leg muscle weakness that had been progressively increasing. Almost a week prior to presentation, she had been started on a five-day course of Ciprofloxacin 500 mg twice a day for urinary frequency and urgency. The remainder of her drug regimen had been stable and she did not use any other over-the-counter drugs or herbal products.

Pertinent lab investigations before starting Ciprofloxacin showed a total leukocyte count of 14,700/uL (4000-11000/uL) with left shift neutrophilia (79%), numerous red blood cells (10/HPF) and white blood cells (4-6/HPF) were seen in routine urine examination. Lipid panel showed total cholesterol 90mg/dl mg/dl (135-200 mg/dl), triglycerides 67 mg/dl (< 150 mg/dl), serum creatinine 0.58 mg/dl (0.6-1.3 mg/dl).

The patient developed insomnia, agitation and

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restlessness a day after starting Ciprofloxacin. Furthermore, she had muscle aches along with muscle weakness in the limbs which worsened over time. She progressively had difficulty in performing the daily activities. The patient required assistance while getting out of bed. Limb weakness progressed while the antibiotic course continued and increased to the extent that she could not keep her balance and experienced fall while walking; with injury to her face and limbs. A CT scan was done by her primary physician (cardiologist) to rule out any neurological pathology, which was normal. She was advised to continue the treatment and was given Risperidone 1mg for insomnia and agitation. Her condition did not improve and the weakness increased to the extent that the patient was unable to walk without support, leading her to seek medical advice from other doctors in the community. She was advised by her family physician to seek immediate care and was subsequently referred in April 2018 for further evaluation.

The pertinent findings on physical examination included reduced power, especially in the lower limbs 3/5 (proximal>distal). Rest of the systemic examination of the cardiovascular, respiratory and abdominal system was unremarkable.

At the time of presentation, the patient's creatinine kinase was found to be slightly elevated 183U/L (normal 29-168) while the hepatic transaminase levels were within normal limits. A provisional diagnosis of statin-induced myopathy due to interaction with Ciprofloxacin was made. The primary treating physician was informed about the probable drug interaction and Atorvastatin and Ciprofloxacin were discontinued after discussion. Muscle weakness resolved over a period of time and the patient showed marked clinical improvement and was able to walk initially with the support of a Zimmer frame and within a period of three weeks, could independently perform daily activities. CK was rechecked to see the trend and to ensure complete resolution. It became normal within two weeks' time. Accordingly, a final diagnosis of drug interaction-induced myopathy due to Atorvastatin-Ciprofloxacin was made. Atorvastatin was restarted after a month.

Discussion

Statins are one of the most widely prescribed groups of drugs worldwide that are generally considered safe and well-tolerated. An important concern is the potential risk of adverse muscular problems; which is further increased with co-administration of a new medicine. The reported incidence of statin-related myopathy is up to 25% in clinical experience; when compared to clinical trials (5%).[4]

In our case, the patient experienced the onset of myopathy as a result of a drug interaction (Atorvastatin-Quinolone-induced) which was associated with the high dose of statins. This case is striking because it describes statin-associated myopathy, which may be dose-related and secondary to a drug interaction between Atorvastatin and Ciprofloxacin that led to significant clinical harm. Only a few reports of statin-quinolones drug interaction have ever been described.[5,6] Exposure to higher doses of statins may play a role as it does not increase the effectiveness in older patients; it rather increases the risk and harm.[7]

There is significant variability in the clinical significance of drug-interaction and their effects are unpredictable. Ciprofloxacin is a weak inhibitor of CYP3A4 from the Quinolone family of antibacterial drugs. It is reported to have a low toxicity and few adverse effects.[8] However, the incidence of myopathy considerably increases when combined with the intake of statins. The exact mechanism is unclear. However, it could be postulated that the co-administration of a newly prescribed drug, that is either metabolised or is cytochrome P450 3A4 inhibitor that interferes with statin metabolism, is associated with an increased risk of myotoxicity; it is directly related to HMG-CoA reductase inhibition and is dose-related.[9] It actually reflects a double hit phenomenon. Other potential causes of deterioration could be age, female gender, ethnicity, genetic predisposition, dose, and polypharmacy,[10] Along with these, high dose of medication can be another factor which can act as a trigger by interfering with its metabolism, and elevates statin concentrations to a toxic range. An animal model of drug-induced rhabdomyolysis using actual clinically used drugs (Quinolone antibacterial drugs and statins) showed that Ciprofloxacin and Atorvastatin combination was most sensitive for the onset of myopathy.[8] Improvement in patient's condition after withdrawal of Ciprofloxacin therapy could explain the phenomena.

The co-prescription of statins and CYP3A4 inhibitors is common in primary care. The development of myopathy upon initiation of Quinolone therapy in the present case raises alarm. The GPs need to be alert because of the possibility of chance association. In light of this, the best practice would be to minimise the risk of harm to the patient by cautious co-prescription, dose adjustments and closer monitoring. Our case represents the importance of close monitoring of patients receiving statins as individual's metabolic capabilities differ. This holds true particularly when they are receiving a new drug that could interact, especially a CYP3A4 inhibitor.

In summary, Atorvastatin is a common option from statin

family for lowering lipid that rarely causes severe myopathy by itself. However, fluoroquinolones (Ciprofloxacin) have been shown to increase it by inhibiting its metabolism. Extreme caution needs to be taken in prescribing these drugs because of chance association.

Conclusion

Myopathy due to drug interaction can have potentially serious outcomes. Quinolone medications should be prescribed cautiously in patients on statin therapy; as they increase the risk of myopathies.

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