Life-threatening rhabdomyolysis following the interaction of two commonly prescribed medications

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CASE REPORT

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Abstract

We report an interaction between erythromycin and simvastatin resulting in life-threatening rhabdomyolysis in an elderly patient. Drugs that inhibit CYP3A4 enzyme can cause elevated serum levels of statins which amplifies the risk of statin-induced rhabdomyolysis. Physicians should be aware of potential drug interactions of statins, which are widely used in the community.

Key Words
Rhabdomyolysis, Drug interaction, Statins, Macrolides

Implications for Practice

1. Muscle injuries are uncommon with statin therapy alone, with a frequency of myalgia (2 to 11%), myositis (0.5%) and rhabdomyolysis (0.1 %).
2. Although the risk of rhabdomyolysis is uncommon with statin therapy alone, it substantially increases with concurrent therapy with strong inhibitors of CYP3A4 such as macrolides.
3. The characteristic triad of warning signs in rhabdomyolysis are muscle pain, weakness and dark urine.
4. Macrolides and statins are two groups of commonly used drugs. Physicians should be aware of the potential drug interactions and avoid concomitant prescription of these drugs. If treatment requires the use of macrolides then consider either stopping statins for a period of time or switch to an alternative statin which is not eliminated by CYP3A4 enzyme.

Background

Statins (HMG-CoA reductase inhibitors) are extensively used in the community to improve lipid profile in dyslipidaemic patients and prevent cardiovascular and cerebrovascular complications.[1] Statins are mainly metabolised by cytochrome P450 3A4 (CYP3A4).

Rhabdomyolysis is a potentially life-threatening condition caused by muscle necrosis and leakage of intracellular muscle contents into the circulation. Although the risk of rhabdomyolysis is uncommon with statin therapy alone, it substantially increases with concurrent therapy with inhibitors of CYP3A4.[2] Large group of macrolide antibacterial agents are inhibitors of CYP3A4 enzyme and have the potential to cause clinical drug interactions.

Case details

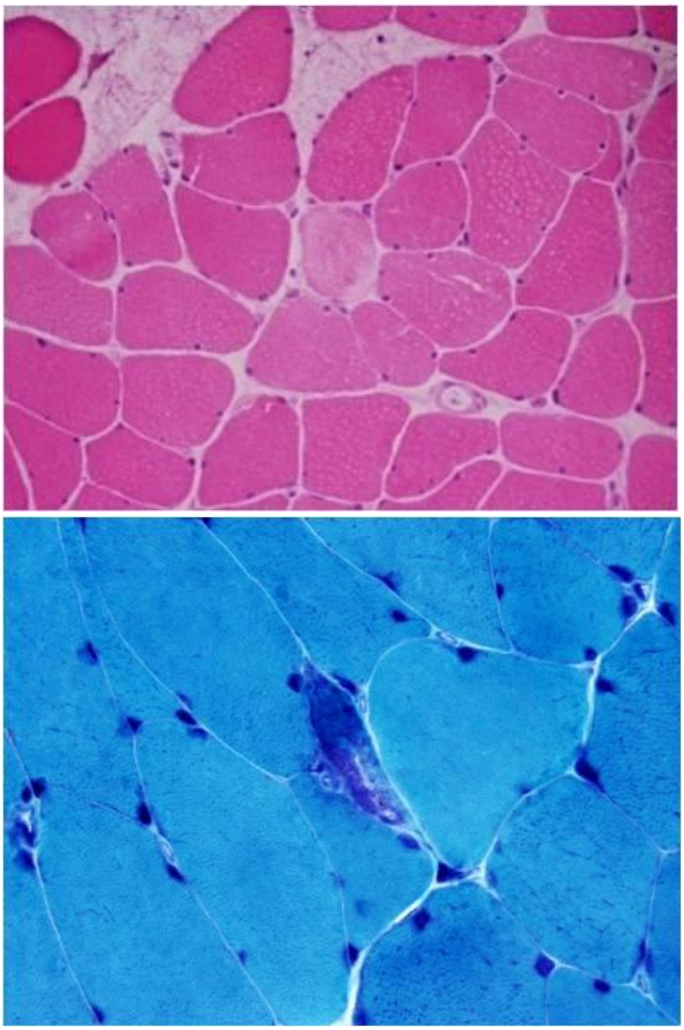
An 85-year-old Caucasian man presented to his general practitioner (GP) with a clinical diagnosis of pneumonia and was treated as an outpatient with erythromycin 400mg twice daily for 10 days. After several days he developed reduced mobility, lethargy, and two episodes of falls at home secondary to generalised weakness, particularly affecting his proximal muscles. The falls were not due to loss of consciousness or any cardiovascular preceding events. Two days after developing muscle weakness he also noted dark red urine. The following day he consulted his GP again and was referred to the Emergency Department.

His medical history was significant for coronary heart disease, hypercholesterolemia, chronic obstructive pulmonary disease (COPD), hypertension, osteoporosis, previous abdominal aortic aneurysm repair, and Ramsay Hunt syndrome. He had unintentionally lost 5kg in weight over the preceding six months due to a change in his diet

since his wife had died. His concomitant drug history included simvastatin 80mg daily, clopidogrel 75mg daily, lansoprazole 30mg daily, tiotropium bromide 18mcg daily, budesonide/efemetrol 400/12mcg twice daily and risedronate 150mg monthly.

Blood tests performed at the time of his first presentation included normal full blood count, electrolytes, renal and liver function tests.

Figure 1: Quadriceps femoris muscle biopsy revealed focal necrotising myopathy and mild to moderate type-IIb muscle fibre atrophy suggestive of statin induced rhabdomyolysis.



A chest CT scan performed prior to hospital admission demonstrated left lower lobe parenchymal inflammatory changes representing infective process with no feature of malignancy. Investigations performed in hospital indicated acute kidney disease (Creatinine 183 µmol/L, Urea 19.1 mmol/L). Serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) were also elevated, with maximum levels of 628 U/L (normal range 10-40 U/L), 561 (10-70 U/L) respectively. Serum creatine kinase (CK) levels increased to a maximum of 23713 U/L and serum lactate dehydrogenase (LDH) of 3515 U/L. Autoantibody screen and the Bence-Jones protein were both negative.

A quadriceps femoris muscle biopsy revealed focal necrotizing myopathy and mild to moderate type-IIb muscle fibre atrophy (Figure 1).

The patient was diagnosed with simvastatin-associated rhabdomyolysis after co-administration of erythromycin. Simvastatin and erythromycin were ceased, and the patient was treated with IV hydration and urine alkalisation with intravenous sodium bicarbonate. The serum CK level and renal function gradually improved. His physical condition improved dramatically and he was discharged home with near normal renal and liver function.

Discussion

Rhabdomyolysis is a potentially life-threatening condition caused by muscle necrosis and extravasation of intracellular muscle contents into the circulation.[3] The release of creatine kinase, potassium, uric acid, myoglobin, calcium and phosphate can result in a spectrum of conditions. [3,4] The severity can range from an asymptomatic elevation in skeletal muscle enzymes to life threatening conditions such as acute renal failure secondary to myoglobinuria or cardiac arrest resulting from hyperkalaemia.[3,4]

Statins (HMG-CoA reductase inhibitors) are extensively used in the community to lower cholesterol.[1] Statins are competitive inhibitors of HMG CoA reductase which is crucial in cholesterol biosynthesis. [5] They are generally well tolerated but have been associated with some rare but severe side effects including myopathy and/or rhabdomyolysis. The mode of action of muscle toxicity is not known and other risk factors include high statin dose, female sex, renal or hepatic impairment, age >70 years and drug-drug interaction.[5,6] The various members of statins have different potentials to interact with other drugs due to their different pharmacokinetic properties.[1] Simvastatin, lovastatin and, to a lesser degree, atorvastatin are metabolized by cytochrome P450 3A4 (CYP3A4) whereas pravastatin, fluvastatin and rosuvastatin are not metabolised by CYP3A4.[5,1]

Macrolides antibiotics are broad spectrum antibacterial used to treat many types of infections.[5] Macrolide antibacterial agents; clarithromycin and erythromycin block the action of CYP3A4 enzyme. Co-administration of these macrolides results in increased level of statins which lead to drug-drug interaction and potential risks. Azithromycin and roxithromycin do not inhibit CYP3A4 and are considered safe to use.

It is noteworthy that co-administration of statins and CYP3A4 inhibitors such as macrolides are associated with increase in the risk of myopathy and rhabdomyolysis. Therefore systematic follow up with blood tests and regular reviews is necessary to prevent harmful and potentially dangerous muscular adverse effects.[7] This is particularly important considering the trend towards more aggressive lipid-lowering therapy and a growing number of older patients using statins. [7]

We believe these pharmacological side effects are usually avoidable if doctors are aware of potential risks of commonly used drugs and their interactions. The risk could be managed either by prescribing non-interacting antibiotics or ceasing statins during antimicrobial treatment.[7]

There are several steps that we can take to reduce statin-associated muscle injuries including making patients aware of the side effects that may be associated with medications they are taking especially co-administration of statins with other medications they have been prescribed. This can be achieved by sufficient communication between patients and the medical staff particularly general physicians and pharmacists.

For hospitalised patients, we should facilitate for the patient to see the hospital pharmacist and have their medications and potential interactions reviewed and explained to them prior to discharge.

We suggest more information should be provided in therapeutic guidelines for physicians to prevent adverse effects and promote monitoring of patients particularly in the case of co-administration of drugs inhibiting CYP3A4 enzyme.

Doctors should be encouraged to use prescribing software program to write electronic prescriptions which automatically checks for common drug interactions. These preventive actions are important not only for increased patient safety, but also for reducing health care cost.

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PEER REVIEW

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PATIENT CONSENT

The authors, Alireza Fallah, Maitri Deep, David Smallwood and Peter Hughes, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.