

## CASE REPORT

# Statin-induced rhabdomyolysis: a complication of a commonly overlooked drug interaction

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## Abstract

Rhabdomyolysis is a well-documented side effect of statin therapy. This risk is increased with concurrent use of medications that inhibit cytochrome p450-3A4 (CYP3A4), such as macrolide antibiotics. We present the case of a 67-year-old patient who was commenced on clarithromycin on a background of simvastatin therapy, resulting in rhabdomyolysis. This case highlights the need for awareness of common drug interactions associated with statins. It also emphasizes the significance of commencing statins at a lower dose in new patients, and lastly, the importance of early recognition and management of rhabdomyolysis to prevent the development of complications.

## INTRODUCTION

Statins are a group of lipid-lowering medications that act by inhibiting HMG-CoA reductase, an enzyme essential to cholesterol synthesis. Statin use is becoming increasingly common, with a rise from 18% in 2003/04 to 26% in 2011/12 in the United States [1]. Given recent recommendations seen in the American Heart Association Practice Guidelines, an increasing number of patients are considered eligible to receive statins to reduce cardiovascular risk [2].

We present a rare case of rhabdomyolysis, complicated by significant acute kidney injury (AKI) and hyperkalaemia, in a patient who was co-prescribed simvastatin and clarithromycin.

## CASE REPORT

A 67-year-old male presented with a 5-day history of worsening myalgia and weakness in his shoulders and lower limbs resulting in reduced mobility. On examination, proximal myopathy was noted with weakness in hip flexion and extension (MRC

Grade 4/5) and in shoulder abduction and adduction (MRC Grade 4+/5). The past medical history included severe chronic obstructive pulmonary disease (COPD) and ischaemic heart disease (IHD).

Initial investigations revealed a creatine kinase (CK) of 62 109 (RI 30–200 U/L), AST 2036 (RI 12–36 U/L), ALT 1145 (RI < 55 U/L), creatinine (Cr) 63 (RI 60–110  $\mu$ mol/L) and potassium 4.4 (SI 3.5–5.2 mmol/L).

Of note, the patient had commenced clarithromycin 250 mg daily 1 month prior to admission following review in the respiratory clinic. This was prescribed on a prophylactic basis to reduce the number of COPD exacerbations. Regular medication included simvastatin 80 mg daily. A presumptive diagnosis of rhabdomyolysis secondary to simvastatin was made and both medications were ceased.

The patient was hydrated intravenously, however, developed AKI, with the creatinine level deteriorating from 63  $\mu$ mol/L on admission to a peak of 325  $\mu$ mol/L on Day 3 (Fig. 1). This was complicated by hyperkalaemia (7.4 mmol/L) requiring repeated treatment with insulin/dextrose and calcium resonium. Calcium

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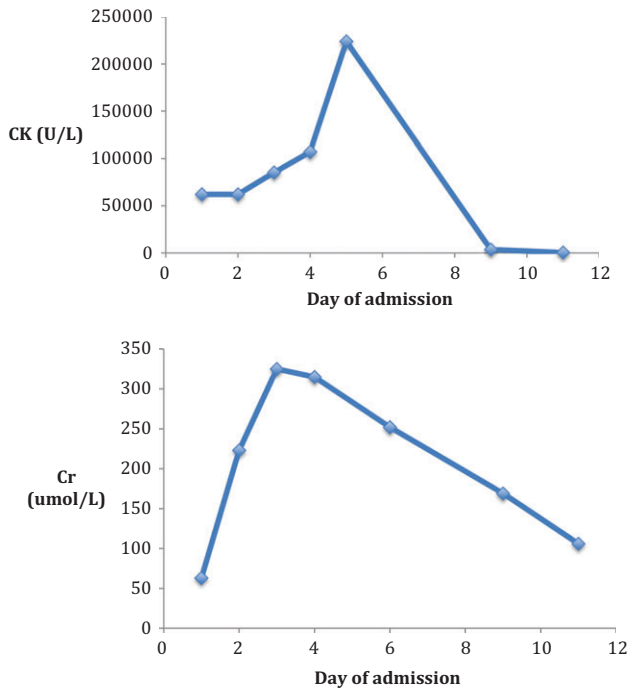


Figure 1: Creatine kinase and creatinine trends.

gluconate was administered for cardio-stabilization due to the significantly elevated potassium despite no acute changes on ECG. The CK continued to rise, reaching a peak level of 223 859 U/L on Day 5 of admission (Fig. 1) with transaminases peaking on Day 3 with an ALT level of 1667 U/L and AST 3123 U/L. Renal replacement therapy was considered, however, avoided as the patient ultimately responded to medical treatment.

The patient’s AKI continued to improve with intravenous fluid therapy and by discharge on Day 11, the creatinine had improved to 106 umol/L (baseline creatinine 63 umol/L) and the CK had improved to 406 U/L. The patient reported significant improvement in shoulder and lower limb myalgia and weakness following physiotherapy and was discharged home after returning to his baseline level of function. Following discharge the patient was commenced on long-term prophylactic doxycycline by his respiratory physician and ezetimibe as an alternative to statin therapy.

**DISCUSSION**

Rhabdomyolysis is a well-documented side effect of statin therapy and this risk is greater with concurrent use of drugs that inhibit cytochrome p450-3A4 (CYP3A4), examples of which are shown in Table 1. These agents reduce the metabolism and consequently increase the serum concentration of CYP3A4-metabolized statins [3]. Other potential causes of rhabdomyolysis are given in Table 2.

Rhabdomyolysis is characterized by the breakdown of skeletal muscle, resulting in the release of sarcoplasmic proteins including AST, ALT and CK and electrolytes. It typically presents with myalgia and muscle weakness of the proximal musculature. Patients may report dark urine as a result of myoglobinuria. The key laboratory finding is an elevated CK five times above the upper limit of normal (RI 30–200 U/L). Potentially life-threatening complications include AKI, hyperkalaemia, compartment syndrome and cardiac arrhythmias. Early rehydration and electrolyte

Table 1: Examples of CYP3A4 inhibitors.

| Drug Class               | Examples  |
|--------------------------|---|
| Antibiotics              | Clarithromycin, Erythromycin, Telithromycin                         |
| Antifungals              | Clotrimazole, Itraconazole, Fluconazole, Ketoconazole, Voriconazole |
| Protease inhibitors      | Atazanavir, Darunavir, Lopinavir, Ritonavir, Tipranavir             |
| Calcium channel blockers | Diltiazem, Verapamil  |
| Others                   | Amiodarone, Cyclosporin, Ranitidine, Sertraline, Tamoxifen          |

Table 2: Causes of rhabdomyolysis

- Trauma
- Drugs and toxins
- Hypo/hyperthermia
- Exertional
- Infections
- Metabolic/mitochondrial myopathies
- Electrolyte abnormalities
- Endocrine disorders
- Idiopathic

correction is essential in preventing complications, as well as addressing the precipitating cause.

One study conducted by the U.S. Food & Drug Administration (FDA) in 2002 examining adverse event reporting suggested that over 50% of cases of statin-induced-rhabdomyolysis were due to drug interactions [4] with a 2012 study, in a UK primary care population showing that 30% of patients were prescribed a CYP3A4 inhibitor in conjunction with a CYP3A4-metabolized-statin during the study period of 1 year [5].

In this case the patient was prescribed 80mg of simvastatin daily; a higher dose associated with an increased risk of statin myopathy. The U.S. FDA does not recommend initiating new patients on a simvastatin dose of 80 mg, to minimize the risk of statin-induced-myopathy and rhabdomyolysis [6].

Clarithromycin is a macrolide antibiotic and a CYP3A4 inhibitor. It has previously been shown to cause rhabdomyolysis in patients taking simvastatin [7]. AKI is a serious complication of rhabdomyolysis and a recent case described a patient requiring haemodialysis for statin-induced-rhabdomyolysis after being prescribed clarithromycin [8]. Both the FDA and the UK Medicines and Healthcare Products Regulatory Agency state that simvastatin is contraindicated in patients taking clarithromycin, erythromycin and telithromycin. Fluvastatin, pravastatin and rosuvastatin may be considered as alternatives as they are not as extensively metabolized by CYP3A4 and therefore less likely to result in rhabdomyolysis but still require careful monitoring [9].

It is estimated that up to 40% of elderly hospital in-patients experience an adverse drug event and that 10% of emergency attendances are due to adverse drug events [10]. This case highlights the need for awareness of important drug interactions in an era of increasing polypharmacy and the morbidity that can result when these interactions are overlooked.

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## CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

## FUNDING

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## ETHICAL APPROVAL

No ethics approval is required.

## CONSENT

We have not identified any direct or indirect potential patient identifiers in our case report. The patient has provided their informed consent for the publication of this case report.

## GUARANTORS

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## REFERENCES

- Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States 2003–2012. *NCHS Data Brief* 2014;**177**:1–8.
- Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**:S46–8.
- Neuvonen PJ, Niemi M, Backman JT. Drug interaction with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006;**80**:565–81.
- Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002;**36**:288–95.
- Bakhai A, Rigney U, Hollis S, Emmas C. Co-administration of statins with cytochrome P450 3A4 inhibitors in a UK primary care population. *Pharmacoepidemiol Drug Saf* 2012;**21**:485–93.
- U.S. Food & Drug Administration (FDA). FDA Drug Safety Communication: New Restrictions, Contraindications, and Dose Limitations of Zocor (simvastatin) to Reduce the Risk of Muscle Injury. Additional Information for Healthcare Professionals. 2011. <https://www.fda.gov/Drugs/DrugSafety/ucm256581.htm> (November 2016, date last accessed).
- Wagner J, Suessmair C, Pfister HW. Rhabdomyolysis caused by co-medication with simvastatin and clarithromycin. *J Neurol* 2009;**256**:1182–83.
- Hill F, McCloskey S, Sheerin N. From a fish tank injury to hospital haemodialysis: the serious consequences of drug interactions. *BMJ Case Rep* 2015;**2015**. doi:10.1136/bcr-2015-209961.
- Williams D, Feely J. Pharmacokinetic–pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002;**41**:343–70.
- Hohl CM, Dankoff J, Colacone A, Afilalo M, et al. Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Ann Emerg Med* 2001;**38**:666–71.