CASE REPORT

From a fish tank injury to hospital haemodialysis: the serious consequences of drug interactions

Fay Joanne Hill,¹ Sarah Jane McCloskey,¹ Neil Sheerin²

¹Renal Department, Newcastle Upon Tyne Hospitals, Newcastle Upon Tyne, UK
²Institute of Cellular Medicine, Newcastle Upon Tyne, UK

Correspondence to

Dr Fay Joanne Hill,
 fayhill@gmail.com

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SUMMARY

We present the case of a 68-year-old man admitted to hospital with severe acute kidney injury secondary to statin-induced rhabdomyolysis. Five weeks previously, the patient started a course of clarithromycin for infection of a finger wound with *Mycobacterium marinum*. His current medications included simvastatin, which he continued along with clarithromycin. The severity of the acute kidney injury necessitated initial continuous venovenous haemofiltration followed by 12 haemodialysis sessions before a spontaneous improvement in renal function occurred. Statins are widely prescribed and we report this case to encourage increased vigilance in avoiding drug interactions known to increase the risk of statin-induced myopathy, including macrolide antibiotics, calcium channel antagonists and amiodarone. The authors would also like to highlight recent guidance on atorvastatin as the statin of choice in patients with chronic kidney disease, and of the need for dose adjustment in those with an estimated glomerular filtration rate less than 30 mL/min/1.73 m².

BACKGROUND

In 2013, Prescription Cost Analysis revealed simvastatin to be the most commonly prescribed drug in England, with 39.9 million prescriptions dispensed that year.^{1 2} While the benefits of this drug in reducing cardiovascular risk are evident, and the side effects relatively rare, the large number of patients taking statins demands particular vigilance towards intolerance and drug interactions.³

Myopathy and muscle disorders are the commonest side effect of statins, with rhabdomyolysis being the most serious.³ We report this case to illustrate the morbidity associated with a case of statin-induced rhabdomyolysis, and to emphasise the ongoing requirement for regular review of statin dosage and medication interactions.

CASE PRESENTATION

A 68-year-old man presented to hospital with a 7-day history of increasing thigh pain and progressive proximal myopathy. Prior to this, he was fit and independent. Medical history included hypertension, hypercholesterolaemia, chronic kidney disease stage 3a, gastro-oesophageal reflux disease and thrombocytopenia of unknown cause, which had been extensively investigated. As a hobby he kept tropical fish.

Six months previously, the patient had been referred to secondary care for a painful ulcer resulting from an injury that he had sustained while cleaning his fish tank. The wound on his left index

finger had failed to heal despite a 3-week antibiotic course. An ultrasound confirmed dactylitis and tenosynovitis. Two wound washouts were subsequently performed 3 weeks apart. At the second procedure, the wound was found to contain locules of pus and *Mycobacterium marinum*, an atypical mycobacterium that is the cause of fish tank granuloma, was isolated on culture.

An antimycobacterial chemotherapy regime was started, consisting initially of rifampicin and ethambutol. On review in clinic 5 weeks prior to this admission, the patient had reported nausea, sore eyes and a bitter taste in the mouth. His symptoms were attributed to rifampicin and this was therefore substituted with clarithromycin; all other medications, including simvastatin 40 mg daily, had remained unchanged.

On admission, physical examination demonstrated a painful proximal myopathy predominantly affecting the lower limbs with no evidence of compartment syndrome. The patient had a healing wound over the ulnar aspect of the distal interphalangeal joint on his left index finger. Cardiovascular, respiratory and abdominal examination was unremarkable; however, the patient was anuric.

INVESTIGATIONS

Biochemistry revealed sodium 137 mmol/L (133–146 mmol/L), potassium 7.0 mmol/L (3.5–5.3 mmol/L), urea 39.8 mmol/L (2.5–7.8 mmol/L), creatinine 702 µmol/L (75–140 µmol/L) and creatine kinase 216 440 U/L (40–320 U/L).

An abdominal ultrasound showed a normal appearance of both kidneys with no evidence of hydronephrosis.

Chest radiograph demonstrated mild left basal atelectasis but the lung fields were otherwise clear, with no evidence of pulmonary oedema.

TREATMENT

The patient was admitted to the intensive care unit and placed on continuous venovenous haemofiltration (CVVHDF). Twenty-four hours later, he was transferred to the renal ward for ongoing management of his acute kidney injury secondary to rhabdomyolysis.

He remained an inpatient for 29 days, requiring 10 further haemodialysis sessions while in hospital. Urine output increased gradually to 800 mLs per day, but then plateaued. Prior to discharge, a tunneled neck line was inserted for outpatient hospital haemodialysis.

Simvastatin treatment was stopped immediately on admission. Antimycobacterial medications were

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also withheld. On review, the left index finger wound was found to have healed with some residual scar tissue and restriction of movement around the proximal interphalangeal joint. The respiratory team advised permanent discontinuation of the clarithromycin and ethambutol course.

OUTCOME AND FOLLOW-UP

Following discharge, the patient required ongoing haemodialysis, but there was evidence of improving renal function with increasing urine output. Three weeks following discharge, his urine output had increased to 1600 mLs/day, creatine kinase had fallen to 161 U/L and dialysis was discontinued. At 3 months from initial presentation, the patient remains dialysis independent. He remains under follow-up due to persistent renal dysfunction ($\text{Cr} > 400 \mu\text{mol/L}$).

He was not restarted on statins. No further antimycobacterial chemotherapy was prescribed.

DISCUSSION

Although the incidence of rhabdomyolysis in patients taking statins is reported to be low (estimated 1.6 cases per 100 000 person-years),³ a systematic review of statin safety noted the importance of preventable cases in those patients taking CYP3A4 inhibitors.⁴ Law and Rudnicka⁴ demonstrated that in cases of rhabdomyolysis linked to simvastatin, lovastatin or atorvastatin, approximately 60% of patients were also taking a CYP3A4 inhibitor, such as a macrolide antibiotic, as in this case.

The risk of statin-induced myopathy is known to be dose dependent,⁵ and therefore drugs that inhibit the CYP3A4 pathway, through which simvastatin is metabolised, potentially increase exposure to the drug and its side effects. The Medicines and Healthcare Products Regulatory Agency (MHRA) published updated guidance in 2012 highlighting that simvastatin is contraindicated with macrolide antibiotics (erythromycin, clarithromycin, telithromycin) due to this risk profile.⁶ Also contraindicated with simvastatin are: azole antifungals (eg, itraconazole), HIV protease inhibitors (eg, nelfinavir), nefazodone, ciclosporin, danazol and gemfibrozil.⁶ In addition, the dose of simvastatin must be restricted to 20 mg maximum if the patient is taking either a calcium channel blocker (amlodipine, diltiazem, verapamil) or amiodarone (table 1).⁶

Recent evidence supports the association between a variant (rs4 149 056) in *SLCO1B1* gene and simvastatin-induced myopathy.⁷ The gene encodes for OATP1B1, which is an organic anion transporter that facilitates hepatic uptake of statins. People who have this variant have reduced transporter function and experience higher blood plasma levels of simvastatin for the same administered dose compared with normal metabolisers.

The Clinical Pharmacogenetics Implementation Consortium have developed prescribing guidelines for simvastatin in patients with the *SLCO1B1* genotype, advising lower doses and routine creatine kinase monitoring for patients known to be heterozygous or homozygous for the decreased-function allele.³ Testing is not yet routinely available in the UK, and the MHRA guidance is that if the genotype is known or can be tested, this should be taken into account when prescribing high doses of simvastatin, but suggest that alternative statins that are not affected by the genotype, should be considered.⁸

Data from The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) collaborative group, which demonstrated the dose-dependent relationship between simvastatin and myopathy, has shown only a 6% reduction in major vascular events in patients taking 80 mg of simvastatin compared to 20 mg.⁹ Therefore, higher doses of

Table 1 Drug interactions associated with increased risk of myopathy/rhabdomyolysis⁶

Interacting agents	Prescribing recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (eg, nelfinavir) Nefazodone Ciclosporin Danazol Gemfibrozil	Contraindicated with simvastatin
Other fibrates (except fenofibrate)	Do not exceed 10 mg simvastatin daily
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed 20 mg simvastatin daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered
Grapefruit juice	Avoid grapefruit juice when taking simvastatin

simvastatin should be reserved for those with severe hypercholesterolaemia and high cardiovascular risk, in whom the benefits outweigh the risks.

Patients with renal impairment are at higher risk of myopathy, and thus their statin dose should be reduced accordingly. The patient presented here, known to have chronic kidney disease stage 3a, should ideally have been on atorvastatin 20 mg at presentation, rather than simvastatin 40 mg, in accordance with National Institute for Health and Care Excellence (NICE) guidance.¹ The statin should then have been suspended when the patient was prescribed a course of clarithromycin.

Learning points

- ▶ Simvastatin is contraindicated with macrolide antibiotics due to increased myopathy risk.
- ▶ *SLCO1B1* genotype can help to predict the risk of statin-induced myopathy but testing is not yet routinely available in the UK.
- ▶ A maximum dose of 20 mg simvastatin should be used in patients also taking amlodipine, diltiazem, verapamil or amiodarone.
- ▶ Atorvastatin 20 mg is the recommended starting agent for patients with chronic kidney disease where statins are indicated.
- ▶ Consider discussing higher statin doses with a nephrologist if the estimated glomerular filtration rate $< 30 \text{ mL/min/1.73 m}^2$.

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