BRIEF COMMUNICATION

HMG CoA reductase-inhibitor-related myopathy and the influence of drug interactions

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Abstract

We report four cases of rhabdomyolysis and severe, disabling myopathy associated with HMG CoA reductase-inhibitor therapy. Patient 1 developed symptoms following the addition of roxithromycin to combination lipid-lowering therapy with simvastatin and gemfibrozil. Patients 2 and 3 became symptomatic after developing acute on chronic renal impairment while taking simvastatin. The muscle biopsy of patient 3 revealed a necrotizing myopathy and the presence of inclusion bodies. Patient 4 developed symptoms within 4 weeks of starting cerivastatin monotherapy. The four cases illustrate the importance of considering the potential for drug interactions and making appropriate dosage adjustments for renal insufficiency in patients receiving HMG CoA reductase therapy. (Intern Med J 2002; 32: 486–490)

Key words: HMG CoA reductase inhibitors, myopathy, renal impairment, rhabdomyolysis.

The use of HMG CoA reductase inhibitors, or statins, has markedly increased since clinical trials convincingly demonstrated efficacy in primary and secondary prevention of coronary artery disease. A rare adverse effect is myotoxicity, with clinical manifestations ranging from asymptomatic serum creatine kinase (CK) elevation to myalgia, rhabdomyolysis and myopathy. Postulated mechanisms for myotoxicity include: (i) mitochondrial dysfunction due to inhibition of mevalonic acid, a precursor of the respiratory chain constituent ubiquinone (co-enzyme Q)2–7 and (ii) increased tyrosine phosphorylation of cellular proteins, resulting in apoptosis and cell death.

The reported frequency of myopathy among patients taking statin monotherapy is approximately 0.2%. The incidence and severity are dose related. Drug interactions also significantly increase the risk. For example, the incidence of myopathy increases to 1% if the HMG CoA reductase inhibitor, lovastatin, is combined with nicotinic acid or a fibric-acid derivative. Small-framed, older patients with renal impairment are particularly prone to combination statin and fibrate-induced myopathy. Patients with low hepatic levels of cytochrome P3A4 (CYP3A4) expression may also be at increased risk. Inhibition of CYP3A4-mediated metabolism of statins by concomitant drug therapy and increased plasma concentrations due to acute or chronic renal failure are similarly associated with an increased likelihood of statin myopathy.

We report the cases of four elderly patients admitted to the Bankstown-Lidcombe Hospital, Sydney, Australia over the past 2 years with rhabdomyolysis and severe, disabling myopathy while taking HMG CoA reductase-inhibitor therapy. In each case, other causes of rhabdomyolysis or a raised serum CK (i.e. hyperkalaemia and hypothyroidism) were excluded.
Case 1
A 73-year-old woman presented with a 3-day history of generalized proximal muscle weakness and myalgia on a background of coronary artery disease, hypertension and hypercholesterolaemia. Her serum cholesterol was 5.4 mmol/L on a combination of simvastatin 80 mg/day and gemfibrozil 600 mg b.i.d, which she had been taking for over 6 months. Her other medications were ramipril, chlorothiazide, diltiazem and aspirin. She had commenced taking roxithromycin for an upper-respiratory-tract infection 7 days prior to the onset of symptoms. Neurological examination revealed grade 4/5 proximal upper- and lower-limb weakness and diffuse muscle tenderness with retained tendon reflexes. Initial serum CK was 9800 U/L (N < 180). Serum urea and creatinine were otherwise normal. Electromyography was within normal limits. Her CK rose to 20 000 U/L, despite cessation of gemfibrozil, simvastatin, diltiazem and roxithromycin. Her urine became dark brown in colour consistent with myoglobinuria. Five days after admission she had grade 2/5 proximal upper- and lower-limb weakness as well as significant neck flexion and extension weakness. Speech and swallowing were unaffected. A left quadriceps muscle biopsy was normal. Her CK normalized 18 days after admission. She was mobilizing with a walking frame at day 24. She had normal strength at discharge, 6 weeks after admission. Her total serum cholesterol rose to 8.0 mmol/L 6 months post-discharge. She was informed of the potential risk of symptom recurrence and consented to the commencement of combination cholestyramine and pravastatin therapy. Serum CK levels and neurological examination remained normal 6 months after the introduction of pravastatin.

Case 2
A 70-year-old woman presented with a 4-day history of severe generalized weakness on a background of type II diabetes mellitus, complicated by chronic renal failure, ischaemic heart disease and gout. Her medications on admission were aspirin, frusemide, captopril, diltiazem, allopurinol and insulin. Simvastatin 20 mg/day had also been commenced 3 months previously. She had a urinary-tract infection and was clinically dehydrated. Neurological findings revealed grade 3/5 proximal upper- and lower-limb weakness, generalized areflexia and a distal sensory loss. Her urine was dark in colour, consistent with myoglobinuria. Serum creatinine and CK levels on admission were 453 mmol/L and 3100 U/L, respectively. Simvastatin was withdrawn. Nerve conduction study findings were consistent with a generalized sensori-motor peripheral neuropathy. Needle electromyography showed spontaneous muscle activity, including increased insertional activity, fibrillation potentials and positive sharp waves. A muscle biopsy of the left quadriceps revealed a necrotizing myopathy (Fig. 1) and the presence of an isolated rimmed vacuole. Serum CK peaked at 5050 U/L and returned to normal within 4 weeks. The patient slowly improved but still required a walking frame for mobilization at discharge 6 weeks post-admission. Motor function was normal at follow up, 1 month post-discharge.

Case 3
An 83-year-old woman presented with a 2-day history of difficulty walking. She had a background of ischaemic heart disease, chronic renal failure, hypertension, peptic-ulcer disease and gout. Nicorandil and candesartan had been withdrawn 2 weeks previously due to acute chronic renal impairment (serum creatinine rise from 230 to 332 mmol/L). A serum CK performed 2 weeks previously was 70 U/L. Medications on admission were pantoprazole, allopurinol, clopidogrel, metoprolol and frusemide. She had also been taking simvastatin 40 mg/day for 5 years. She demonstrated grade 4/5 upper limb and 3/5 lower-limb proximal-muscle weakness. Urine was positive for myoglobin. Simvastatin was ceased. Initial CK was 3200 U/L and peaked at 11 300 U/L 6 days later. Electromyography showed small, brief duration and polyphasic motor units consistent with a myopathy. A muscle biopsy revealed muscle necrosis and four of 20 muscle fibres seen in the biopsy specimen contained rimmed vacuoles under light microscopy (Fig. 1). Electron microscopy confirmed the presence of tubulo-filamentous inclusion bodies (Fig. 2). Oral prednisolone 30 mg/day was commenced. She was able to mobilize short distances with a frame 14 days after admission, at which time her CK had normalized and her serum creatinine improved to 235 mmol/L. Corticosteroid therapy was withdrawn on discharge. However, proximal muscle weakness persisted and she was still unable to weight-bear without assistance on last review, 6 months post-discharge.

Case 4
A 78-year-old woman presented with a 2-week history of increasing difficulty walking and myalgia on a background history of diabetes mellitus and hypertension. Her medications on admission were metformin, glipizide, aspirin and irbesartan. She had also commenced cerivastatin 20 mg/day 1 month prior to admission. She had grade 4/5 upper-limb
and 3/5 lower-limb proximal muscle weakness. Urine was positive for myoglobin. Initial serum creatinine and CK were 50 mmol/L and 17 400 U/L, respectively. Cerivastatin was ceased. Electromyography showed spontaneous muscle activity, including: (i) increased insertional activity, (ii) complex repetitive discharges, (iii) fibrillation potentials and (iv) positive sharp waves. A muscle biopsy showed non-specific type 11 fibre atrophy. The patient rapidly improved and was mobilizing 4 days after admission. The serum CK was normal at discharge, 10 days post-admission.

An increase in plasma concentrations of HMG CoA reductase inhibitors by inhibition of CYP450-mediated metabolism has become recognized as an important contributory factor in the development of statin-related myopathies.\textsuperscript{1–4} Inhibition of non-cytochrome P450-mediated pathways may also contribute, as seen in the case of gemfibrozil, which increases plasma concentrations of simvastatin and its active form, simvastatin acid, in healthy volunteers.\textsuperscript{13} Lovastatin, simvastatin, atorvastatin and cerivastatin are primarily metabolized by CYP3A4. Fluvastatin is predominantly metabolized by CYP2C9 and pravastatin undergoes non-CYP450 hepatic sulphation metabolism.\textsuperscript{1} There are several case reports of rhabdomyolysis or myopathy in patients taking a statin in combination with other CYP3A4-inhibitors, including: (i) erythromycin, (ii) clarithromycin, (iii) cyclosporin, (iv) diltiazem, (v)itraconazole and (vi) nefazodone.\textsuperscript{1–4,14} Roxithromycin is a macrolide antibiotic that has a much lower affinity for CYP3A4.

Figure 1 Parts (a) and (b) from the muscle biopsy of patient 2 show scattered necrotic muscle fibres (see arrows) and a positive acid-phosphatase reaction in macrophages consistent with a necrotizing myopathy. Parts (c) and (d) from the muscle biopsy of patient 3 show a group of fibres containing inclusion bodies and a typical rimmed vacuole. The pathological features of necrotic fibres and inclusion bodies characteristic of a necrotizing myopathy and inclusion body myositis were seen in the muscle biopsies of patient 3.
than erythromycin or clarithromycin. Nevertheless, it has been shown to increase plasma concentrations of other CYP3A4-metabolized drugs, most notably cyclosporin. Our first patient is the first reported case of an adverse drug interaction between simvastatin and roxithromycin. Although gemfibrozil and diltiazem were likely contributing factors, she had been taking them for more than 6 months and her myopathy did not develop until after she commenced roxithromycin. This indicates that roxithromycin was likely to be an offending agent. Successful rechallenge of an offending statin agent has been previously reported in a patient taking lovastatin. We were reluctant to re-institute simvastatin in this patient, due to her requirement for indefinite treatment and our concerns of the risk of recurrence if another CYP3A4-inhibitor was added. Hence, pravastatin was chosen. Thus far, her symptoms have not recurred.

All four of our patients were severely disabled. Three of the patients recovered fully, consistent with the clinical outcomes reported in the majority of patients with statin-related myopathy. Muscle biopsy findings in one of our four patients revealed both a necrotizing myopathy indicative of myotoxicity and the presence of inclusion bodies. Patient 3 was still unable to mobilize independently at last follow up, 6 months post-discharge. It is quite possible that the ‘inclusion bodies’ seen in patient 3 were incidental and unrelated or that they fell within the spectrum of pathological changes seen in statin myopathies.

There have been isolated cases of polymyositis and mitochondrial myopathy in association with HMG CoA reductase therapy. We are unaware of any previous report of inclusion-body myositis presenting in a patient taking statin therapy. We are unaware of any previous reports of ‘inclusion bodies’ in muscle biopsies of patients presenting with a statin myopathy. The idiopathic inflammatory myopathies – inclusion-body myositis and polymyositis – most commonly evolve chronically over months or years, whereas dermatomyositis may present acutely over days or weeks. Acute rhabdomyolysis and myoglobinuria are rare in all three subtypes. Nevertheless, a third alternative explanation for patient 3 is that simvastatin contributed to the development of acute rhabdomyolysis, most probably as a result of increased blood concentrations due to acute on chronic renal impairment. This, in turn, unmasked an underlying muscle disorder, namely inclusion-body myositis, which remained clinically symptomatic. Patient 3 illustrates the importance of considering a muscle biopsy in patients with rhabdomyolysis and severe myopathy suspected to be related to HMG CoA reductase-inhibitor therapy.

The cases of patients 2 and 3 also highlight the importance of appropriate statin dosages in severe renal insufficiency. The renal excretion of simvastatin is 13% of an absorbed dose. Lovastatin, pravastatin and cerivastatin also have >10% renal excretion, whereas fluvastatin is <6% and atorvastatin is 2% renally excreted. The recommended starting dose of simvastatin in patients with chronic renal failure is 5 mg/day. Patient 2 was also taking diltiazem, and it is feasible that her plasma simvastatin concentrations may have been significantly lower had she been taking simvastatin monotherapy and had normal renal function. Patient 4 developed a statin myopathy in the context of normal renal function and polypharmacy, although she was not taking a concurrent CYP3A4-inhibitor.

Approximately 0.1–0.5% of patients taking lipid-lowering agents will develop an elevated serum CK. We do not routinely check serum CK before therapy, in part because of differences in normal ranges between laboratories and in part because serum CK levels have a non-Gaussian distribution, with the long-tail skewed towards higher levels. However, we routinely monitor serum CK after starting patients on

Figure 2  Electron microscopy of muscle fibres from patient 3, showing cytoplasmic aggregates of tubulofilamentous structures.
l lipid-lowering therapy, usually at the same time post-treatment that serum cholesterol and triglyceride levels are measured. In clinically asymptomatic patients in whom serum CK has risen above the normal range, we would recommend allowing an elevation up to three times the upper normal value before considering withdrawal.19

In conclusion, we report two unique findings: (i) HMG CoA reductase-inhibitor-related myopathy associated with roxithromycin therapy and (ii) the presence of ‘inclusion bodies’ in the muscle biopsy of a patient presenting with inclusion-body myositis manifesting as acute rhabdomyolysis and severe muscle weakness in the context of a patient taking a HMG CoA reductase-inhibitor therapy. Our four cases highlight the potential of hepatic drug interactions and the need to make appropriate dosage adjustments for renal insufficiency in patients receiving HMG CoA reductase-inhibitor therapy.

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