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CASE REPORT

Presumed interaction of fusidic acid with simvastatin

A. J. Burtenshaw,[1] G. Sellors[2] and R. Downing[3]

1 Specialist Registrar, Anaesthesia & Intensive Care Medicine, 2 Consultant in Anaesthesia & Intensive Care Medicine, 3 Consultant in Vascular Surgery, Worcestershire Royal Hospital, Charles Hastings Way, Newtown Road, Worcester WR5 1DD, UK

Summary

A 63-year-old man was admitted 6 weeks after an elective abdominal aortic aneurysm repair following which methicillin resistant *Staphylococcus aureus* (MRSA) had been cultured from the aneurysmal sac. He had been commenced on a course of fusidic acid at discharge in addition to his ongoing statin prescription and presented 4 weeks later with symptoms consistent with rhabdomyolysis. Severe rhabdomyolysis was confirmed and despite prolonged and complicated critical care management, his treatment was unsuccessful. Extensive investigations ruled out other known causes of this clinical presentation and failed to identify any other precipitating cause of rhabdomyolysis. We believe the most likely cause was hepatic inhibition of the CYP3A4 hepatic isoenzyme by fusidic acid resulting in an acute severe rise in plasma simvastatin level and extensive myocellular damage. Increasing MRSA colonisation and infection rates together with increased statin usage have the potential to increase the incidence of this presumed drug interaction.

Correspondence to: Dr A. J. Burtenshaw
E-mail: andrew_burtenshaw@doctors.org.uk
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The association of statins with rhabdomyolysis is well known. Although exact mechanisms remain uncertain, specific drug combinations are thought to result in particularly severe and often fatal presentations and this has previously resulted in drug withdrawal from the market. This case report outlines a case of presumed interaction of fusidic acid with simvastatin resulting in an extreme degree of rhabdomyolysis. Extensive morbidity with ultimate mortality and considerable resource consumption resulted. In a climate of increasing MRSA infection rates and escalating statin usage, we believe this drug combination may potentially cause considerable harm and has relevance to a wide range of specialty areas.

Case report

A 63-year-old man was admitted having been bed-bound for 1 week with a history of dark urine, lower back pain, myalgia and symmetrical peripheral muscle weakness affecting both upper and lower limbs. His past medical history included hypertension, hypercholesterolaemia, a posterior circulation transient ischaemic attack and ataxic gait. He had stopped smoking cigarettes 8 years previously. The patient's usual medication included desloratidine, enalapril, dipyridamole, aspirin, bisoprolol, ranitidine, diclofenac and simvastatin.

Six weeks previously he had undergone elective repair of a 6 cm diameter infra-renal aortic aneurysm. Three doses of prophylactic vancomycin, cefuroxime and metronidazole were given peri-operatively. According to local practice, simvastatin was discontinued 7 days prior to surgery and restarted 2 weeks postoperatively. Preoperative blood tests revealed normal serum cholesterol and renal function.

A methicillin resistant strain of *Staphylococcus aureus* (MRSA) was cultured from the contents of the aneurysm sac, but not from subsequent blood culture samples. He was given a 5-day course of intravenous vancomycin and discharged on a 3-month course of oral fusidic acid to cover the MRSA isolate. Serum biochemistry was normal at discharge.

He was re-admitted 32 days after discharge. On examination, muscle power was medical research council (MRC) grade 2/5 proximally in the lower limbs, and 3/5 proximally in the upper limbs. There was distal sparing with MRC grade 5/5 power in hands and feet.

An urgent MRI scan revealed no evidence of spinal cord compression.

Serum creatinine kinase concentration was 113 040 $IU.l^{-1}$. Urinalysis revealed myoglobinuria. Serum potassium concentration was 6.5 $mmol.l^{-1}$. Arterial blood base excess was -7.6 $mmol.l^{-1}$ and arterial ionised calcium 0.65 $mmol.l^{-1}$.

The diagnosis of acute renal failure secondary to rhabdomyolysis was made and he was transferred to the intensive care unit. In view of the worsening metabolic derangement continuous veno-venous haemodiafiltration was initiated.

Three days later muscle power was MRC grade 0/5 proximally in the upper and lower limbs. The distal sparing persisted with 5/5 power in hands and feet. Diaphragmatic function was dramatically reduced and he demonstrated tachypnoea and an inability to cough. He progressed to require tracheal intubation and subsequent percutaneous tracheostomy.

Concurrent with intubation serum creatinine kinase concentration exceeded the laboratory assay limit of 450 000 $IU.l^{-1}$. Autoimmune screen and short synacthen tests were normal. Muscle biopsy demonstrated widespread necrosis and a generalised reduction in muscle enzyme activity, including a mild deficiency of carnitine palmitoyl transferase consistent with rhabdomyolysis. Nerve conduction studies were normal. An electromyogram (EMG) demonstrated no spontaneous activity.

A rheumatology review noted no cutaneous lesions to suggest dermatomyositis, and autoimmune myositis was considered unlikely. Serum was sent for coxsackie virus, Epstein–Barr virus, influenza, adenovirus and toxoplasmosis immunology screens, all of which returned negative results.

The causes of rhabdomyolysis are diverse. Nevertheless, exclusion of all other likely causes lends support to the association of rhabdomyolysis with the combination of simvastatin and fusidic acid. In particular, the patient had no signs suggestive of limb ischaemia, had not suffered trauma, carbon monoxide poisoning or been exposed to heat injury or the effects of excessive physical exertion. No viral or bacterial causes of rhabdomyolysis were identified. Endocrine causes of rhabdomyolysis were excluded (diabetic ketacidosis, thyrotoxicosis, hypophosphataemia and hypokalaemia) and the patient denied ingestion of any illicit drugs known to be associated with rhabdomyolysis. It was, therefore, considered likely that the disease was related to his medication. Although he had previously been taking simvastatin at the same dose for 10 years, the only medication change was the addition of fusidic acid to treat MRSA.

This patient had been on a number of drugs prior to surgery, most of which had been restarted in the postoperative phase. Of these, simvastatin is strongly suspected to have been the cause, with fusidic acid acting as a potentiator by inhibiting the metabolism of simvastatin. Although desloratidine has also previously been implicated in rhabdomyolysis, this drug had not been restarted in the postoperative period.

He began taking this combination 2 weeks after surgery yet presented to hospital 4 weeks later. It is postulated that this time interval occurred before presentation because inhibition of metabolism resulted in slow accumulation of simvastatin, which took some time to reach a threshold at which rhabdomyolysis resulted. Subsequently there was a secondary delay representing the period of development of rhabdomyolysis prior to presentation to hospital.

Four days after admission to intensive care, he required emergency splenectomy for spontaneous splenic rupture. Histology of the spleen demonstrated multiple areas of acute infarction, and no evidence of viral inclusions. Unfortunately he sustained a peri-operative myocardial infarction, with a rise in troponin T to 3.0 $\mu g.ml^{-1}$. This was complicated by profound rhythm disturbance including multiple asystolic periods which necessitated insertion of a permanent pacemaker. He subsequently developed ischaemic colitis and because of excessive transfusion requirements, exacerbated by the anticoagulation required for CVVHDF, he underwent subtotal colectomy and ileostomy.

Throughout all of these complications his ventilatory requirements varied between pressure support ventilation and short but non-sustained periods utilising a tracheostomy mask alone. Nevertheless, his ability to cough remained poor, and by this stage he had no power in his limb muscles, and very limited facial muscle power. He had required renal replacement therapy throughout his admission.

After 140 days of supportive treatment he had regained only minimal distal power (MRC grade 2/5 in upper limbs distally, 0/5 proximally), and repeat nerve conduction studies were undertaken: These revealed evidence of a severe sensorimotor neuropathy consistent with critical care neuropathy. Treatment continued during which time limited muscle power improvement was noted, particularly distally in both upper and lower limbs, and in facial muscle power. Sadly, he subsequently died as a result of haemorrhage from tracheal granulomata associated with his tracheostomy.

Discussion

Rhabdomyolysis is a rare complication of statin monotherapy with an incidence of 0.44 per 10 000 person years

of exposure and a 1-year number needed to harm of 22 700 for each of atorvastatin, pravastatin and simvastatin [1]. The number of prescriptions for lipid lowering agents in the UK has risen dramatically from 9.0 million in the year 1999–2000 to 34.1 million in 2005 [2]. Whilst cerivastatin (now withdrawn) posed a 10-fold increase in risk as monotherapy, it was in combination with gemfibrozil that it produced an incidence of rhabdomyolysis of 1000 per 10 000 person years, or a 1-year number needed to harm of only 10. The combination of atorvastatin or simvastatin with a fibrate produced an incidence between 17 and 23 per 10 000 person years.

The combination of fusidic acid with simvastatin has previously been suggested as a rare potential cause of rhabdomyolysis [3]. It is thought that since both these drugs are metabolised via the CYP3A4 isoenzyme, the enzyme inhibiting effect of fusidic acid causes an acute severe rise in the levels of simvastatin, which otherwise has a low rate of rhabdomyolysis. Other drugs that are known to increase serum levels of statins via CYP 3A4 inhibition include the macrolide antibiotics, azole antifungal agents, amiodarone and grapefruit juice. The degree of rhabdomyolysis potentially associated with the combination of simvastatin and fusidic acid appears to result in particularly profound muscle damage.

Proposed mechanisms of muscle damage imply a multifactorial pathogenesis. It may result from a combination of interrupted glycoprotein synthesis and deficiency in chloride channel action in the muscle membrane, intramyocellular hypercalcaemia impairing membrane function or reduced cholesterol levels impairing Na^+/K^+ channel function. These actions bring about initial myocellular damage causing local creatinine kinase production, which is an enzyme which results in the release of ATP. Massive CK rises will therefore produce huge ATP release followed by depletion of ATP stores; the shortage of ATP acts as a secondary insult compounding the initial muscle damage [4].

We were unable to identify whether there have previously been any long term survivors following rhabdomyolysis of this severity.

It is clearly impossible to be certain of the aetiology of rhabdomyolysis in each individual case, particularly in the context of multiple pharmacological agents. However, we believe that the body of literature relating rhabdomyolysis with statins means that the likelihood of simvastatin being implicated in this case is very high. The addition of fusidic acid fits with our presumption on chronological grounds, having been recently commenced, and also on pharmacological grounds, there being a viable explanation for potentiation of statins via inhibition of CYP3A4 in concurrent literature. Although there are examples in the literature of a proposed association between rhabdomyolysis and enalapril, and also independently with aspirin, these have been associated with mild rhabdomyolysis only, and do not share features with this case. In particular, the proposed mechanism implicating enalapril was that of induction of hyponatraemia (which did not exist as a presenting feature in this case) resulting in subsequent cellular damage. Aspirin has only been associated with rhabdomyolysis in the context of overdosage. It is for these reasons that we believe the combination of simvastatin and fusidic acid to be the most likely cause for this case of rhabdomyolyis.

We live and work in an increasingly cholesterol aware society in which the use of statins is growing not only from prescriptions, but also from newly available 'over the counter' preparations. Although previously documented in a small number of case reports [3–7], the interaction of simvastatin with fusidic acid remains relatively unknown. Nevertheless, increasing intake of statins together with increasing MRSA detection rates and MRSA public concern suggests that the previously rarely prescribed drug combination of a statin and fusidic acid may become much more common, as may any relationship this bears to the development of rhabdomyolysis.

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