Sodium fusidate with simvastatin silencing muscles

Angelos Assiotis\textsuperscript{a}, Ptolemaios Georgios Sarrigiannis\textsuperscript{b}, Robin Highley\textsuperscript{c} and Marios Hadjivassiliou\textsuperscript{a}

\textit{\textsuperscript{a}Department of Neurology, \textsuperscript{b}Department of Neurophysiology, \textsuperscript{c}Department of Neuropathology, Royal Hallamshire Hospital, Sheffield, UK}

Corresponding address: Dr Angelos Assiotis, Core Surgical Trainee, Department of Trauma and Orthopaedics, Queen’s Hospital, Romford, Flat D, 16 Holland Road, London, W14 8BA, UK. Email: aassiotis9@hotmail.com

Date accepted for publication 11 September 2010

Abstract

A 73-year-old lady became bed bound with progressive generalized weakness 2 weeks after the introduction of sodium fusidate for osteomyelitis. She was already on simvastatin for years. Electromyography showed no spontaneous muscle activity from any of the muscles sampled. The temporal relationship of symptom onset after introduction of fusidic acid and full recovery after cessation of the 2 drugs suggests a serious interaction that deserves wider recognition.

Keywords

Statin; fucidic acid; rhabdomyolysis.

Case report

A 73-year-old lady was transferred to the neurology unit from a District General Hospital (DGH), with a 2-week history of progressive limb weakness resulting in frequent falls. Her admission was precipitated by her inability to walk and to feed herself due to severe proximal muscle weakness. She had become bed bound and complained of reduced appetite and nausea, which she linked to the introduction of antibiotics prescribed by the hospital doctors.

Past medical history included type II diabetes mellitus, breast cancer, osteoarthritis, hypercholesterolemia and hypothyroidism. Her medication included sodium fusidate, levothyroxine, metformin, amitriptyline and simvastatin, which she had been taking for many years. Sodium fusidate had been prescribed 1 week before the onset of the weakness, in order to treat osteomyelitis in her a right big toe diagnosed at the diabetic clinic.

Clinical examination revealed reduced tone in all 4 limbs with reduced strength more marked proximally and ranging from 2/5 to 3–4/5 more distally. Her reflexes were reduced or absent and her plantars were flexor. She had normal sensation and denied any muscle tenderness. The rest of the neurological examination was normal.

Brain and cervical spine magnetic resonance imaging was normal, as was cerebrospinal fluid examination. Urine dipstick test was positive for blood (++++) and her creatine phosphokinase (CPK) level was increased to 80,000 U/L (normal range <210 U/L). Both the statin and the sodium fusidate were stopped.
The first neurophysiological assessment was performed 3 weeks after symptom onset. Sensory and motor nerve conduction studies showed no evidence of large fibre peripheral neuropathy. The amplitude of the compound muscle action potentials recorded from the intrinsic foot muscles and the right hand were normal. Electromyographic (EMG) examination showed predominately short duration and low amplitude outliers in the right vastus lateralis, the biceps brachii and the deltoid. An early recruitment with a low amplitude envelop of the recruitment pattern (<1 mV) appeared in the aforementioned muscles. Despite several needle insertions in all the examined muscles, no spontaneous activity could be detected over proximal or distal muscles. She underwent a muscle biopsy. This showed widespread polyfocal rhabdomyolysis. The fibbers varied in morphology from normal, necrotic (with and without macrophage permeation) to early regeneration (Fig. 1). There was no evidence of inflammation.

The patient's renal function started deteriorating whilst on the neurology ward with increased creatinine and urea levels. The increased potassium level did not respond to pharmaceutical interventions and the patient was therefore transferred to the Renal Unit for renal dialysis. She remained there for 7 weeks requiring regular dialysis. Her renal function gradually improved and once the patient was no longer dependent on dialysis she returned to the neurology unit for physiotherapy. Her CPK returned to normal. She appeared to have significant improvement of power in her arms (grade 4/5) with some residual weakness in her legs (grade 3/5). At this stage she was able to feed herself but could not walk. The patient had a repeat EMG performed at this stage of recovery (i.e. 2 months after the onset). This assessment showed a significant drop in the amplitude of the recorded potentials from the intrinsic foot muscles particularly from the extensor digitorum brevis. The associated deep peroneal and tibial conduction velocities were marginally reduced. The sensory responses were also considerably reduced in amplitude, compared with the previous examination but the amplitude of the responses from the right superficial radial and the sural nerves were well within normal limits, in absolute terms. Hence, there was evidence of a superimposed mild axonal peripheral neuropathy. This was felt to be the result of her critical illness and her renal failure. EMG of the right deltoid showed several polyphasic, unstable motor unit potentials suggesting motor unit regeneration. The recruitment pattern was now significantly increased in amplitude in different areas of the muscle. Some fibrillations and positive sharp waves were seen in some of the needle insertions on this occasion. No significant changes were seen in the recruitment pattern of the right vastus lateralis compared with the previous examination with the exception of several polyphasic potentials.

The patient continued to improve and was discharged 3 months after her admission. At this stage she was able to walk with walking aids. She was reviewed in the clinic 6 months after discharge at which stage she was back to normal without any residual weakness.

**Clinical evidence**

This case report provides detailed serial neurophysiological assessments of the silent muscle after acute toxic insult from the combination of fusidic acid and simvastatin. The very small
duration, low amplitude motor unit potentials with the very low amplitude early recruitment pattern observed only over proximal muscles and the absence of any form of spontaneous activity 3 weeks after the onset of weakness seem to be the characteristic EMG changes that correlated well with the clinical picture. Follow-up EMG at 2 months showed features suggestive of motor unit regeneration, more significant in the upper limbs. This again correlated with the clinical picture of improvement of the arm function before the improvement of the patient’s mobility. The temporal relationship between the onset of this patient’s symptoms and the introduction of sodium fusidate led us to conclude that the statin–fusidate interaction was the sole cause of the rhabdomyolysis and subsequent acute renal failure. Further confirmation of the aetiology of the rhabdomyolysis relates to the successful outcome (full recovery) following early recognition and withdrawal of the causative agents.

Although a causal relationship between statins and muscle disease is widely known, rhabdomyolysis is a rare adverse event occurring only in 0.44 per 100,000 person years of exposure[1]. In a so-called cholesterol-sensitive society, statin prescription is always on the increase. Furthermore, statins have been granted licensing to be marketed as over-the-counter drugs. Fusidic acid is also becoming a favourite drug in the treatment of *Staphylococcus aureus* infections, a frequent pathogen. A review of the current literature revealed a small number of previous case reports suggesting that the interaction between a statin, mainly simvastatin or atorvastatin, and fusidic acid could potentially cause rhabdomyolysis[2–6].

Such reports, however, provided limited information on the EMG changes associated with rhabdomyolysis.

The mechanism behind the effects of HMG-CoA reductase inhibitors, of which simvastatin is one, on muscle remains unclear. It has been suggested that statins cause reduced cholesterol levels resulting in impaired Na\(^+\)/K\(^+\) channel function and membrane instability[7]. This results in increased intracellular calcium which in turn initiates apoptosis, impaired chloride channel action and interruption of glycoprotein synthesis[8]. Although myotoxicity is said to be a dose-related effect, simvastatin-related rhabdomyolysis is actually a rare adverse event because therapeutic blood levels are not usually injurious to muscle[9]. The frequency may well increase as the trend is for ever-increasing doses of the drug in order to achieve desirable lower levels of cholesterol. There is one report of rhabdomyolysis occurring after a single dose of a statin, suggestive of an idiosyncratic reaction[10]. On the other hand, rhabdomyolysis can occur up to a year after the introduction of the drug without alteration of the dose but with progressive muscle discomfort and weakness noted by the patient but frequently ignored by the treating physician. Potentially harmful blood levels of the drug can also be the result of another administered drug that inhibits the catabolic pathway of statins via the CYP 3A4 system. Such known CYP 3A4 inhibitors include macrolides, azole derivatives and grapefruit juice. Although fusidic acid is not a widely recognized CYP 3A4 inhibitor, it can inhibit certain isoforms of the enzyme[11].

Needle EMG abnormalities in the inflammatory myopathies are well documented but only limited data are available on acute necrotizing myopathies with even less data on statin-related acute rhabdomyolysis. One report retrospectively described the results of EMG performed during the first 2 weeks from the onset of symptoms in 15 patients with acute rhabdomyolysis (only one patient was on simvastatin but was also taking cyclosporine). They concluded that EMG findings were often normal and when abnormal, the changes were subtle with no spontaneous activity at rest and no correlation to the level of creatine kinase (CK) increase[12]. Another study reported 5 cases of statin-related myopathies that were characterized by the absence of significant histopathological findings despite severe weakness and high CK values. Muscle biopsy results in 4 of their cases showed type II muscle fibre atrophy but little or no necrosis. Three of the 5 patients were also being treated with cyclosporine. On EMG there were features consistent with myopathy in all cases[13]. Similar biopsy findings were reported in a single case report in which rhabdomyolysis was presumed to be the result of lovastatin–gemfibrozil combination. However, the EMG of this case showed fibrillation potentials, complex repetitive and myotonic discharges, with motor unit potentials and recruitment pattern abnormalities indicating a myopathic process[14]. Muscle fibre necrosis was only described in the muscle biopsies of 2 further cases in which rhabdomyolysis followed a combination treatment of lovastatin–gemfibrozil and simvastatin–ketoconazole[15,16]. EMG was available in one of the cases and showed myopathic abnormalities with fibrillations and positive sharp waves[15].

In summary, this report highlights a potentially devastating interaction between fusidic acid and a statin resulting in severe necrotizing myopathy. The striking EMG data correlate well with the clinical picture from the onset to recovery.
Teaching points

- Complete tetraparesis can be secondary to muscle pathology
- Rhabdomyolysis can be the result of drug interaction
- Identification of the cause and the early withdrawal of the offending drug may result in complete recovery

References