

SHORT REPORT

Peripheral neuropathy associated with simvastatin

T Phan, J G McLeod, J D Pollard, O Peiris, A Rohan, J-P Halpern

Abstract

Four patients are described who developed sensorimotor neuropathy while being treated with simvastatin and had complete or partial resolution of clinical abnormalities after withdrawal of treatment. In one case onset was within days of commencing treatment, but in two cases symptoms did not develop for two years. The electrophysiological and pathological features of the neuropathy were those of axonal degeneration. Clinical evidence of proximal and distal weakness and muscle fasciculations and persistent abnormalities of sensory conduction after recovery suggest the possibility of toxic damage to anterior horn cells and dorsal root ganglia. Thirty eight other cases with symptoms suggestive of peripheral neuropathy have been reported to the Australian Adverse Drug Reactions Advisory Committee, 22 of whom recovered after cessation of treatment; in five cases there was recurrence after re-exposure to the drug. Simvastatin should be considered among the causes of peripheral neuropathy, and the drug should be withdrawn if patients receiving it develop muscle weakness or sensory disturbances.

(*J Neurol Neurosurg Psychiatry* 1995;58:625-628)

Keywords: sensorimotor neuropathy; simvastatin

Simvastatin is a cholesterol lowering drug that acts by inhibiting hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol synthesis.¹ Other drugs in this class include lovastatin and pravastatin. Common minor adverse effects reported in early clinical trials were headaches and non-specific gastrointestinal complaints.^{2,3} Abnormal laboratory findings included transient increases in serum transaminase and serum creatine kinase (CK).²⁻⁴ A myopathic syndrome consisting of diffuse myalgia, muscle tenderness, and weakness associated with a rise in serum CK has been described.^{2,5} Rarely there is progression to rhabdomyolysis and acute renal failure from myoglobinuria.⁶ Neurological side effects listed by the manufacturer include

cranial nerve dysfunction, tremor, vertigo, memory loss, paraesthesiae, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, and depression. To our knowledge, however, there have been no documented cases reported of peripheral neuropathy associated with simvastatin. We present here four patients with clinical and electrophysiological evidence of a peripheral neuropathy after treatment with simvastatin; in all cases there was symptomatic improvement after withdrawal of the drug.

Case reports

CASE 1

A man aged 52 started treatment with simvastatin (10 mg/day) 12 months before neurological assessment. He did not smoke tobacco and drank only 20 g of alcohol a week. Soon after starting to take the drug he noticed generalised muscle weakness and fatigue. The weakness became progressively worse and he had difficulty in ascending stairs and running. After six months his right and subsequently his left foot became numb. On examination the cranial nerves were intact. There was no muscle wasting; there was mild distal weakness in the lower limbs and he had difficulty in rising from a squatting position. Ankle jerks were absent but other reflexes were present and the plantar responses were flexor. Coordination was normal, light touch and temperature sensation were impaired on the dorsum of the feet, vibration sensation was impaired at the toes, and two point discrimination was profoundly impaired on the feet.

Haemoglobin, white cell count, erythrocyte sedimentation rate, blood glucose, serum electrolytes, liver function tests, blood urea, serum creatinine, thyroid function studies, glucose tolerance test, serum proteins, anti-nuclear antibodies, serum vitamin B6, B12, and folic acid concentrations, HIV and hepatitis B serology, serum and urinary electrophoresis, and tests for cryoglobulins and urinary heavy metals and chest radiograph were all normal or negative. Serum CK concentration was 900 U/l. Treatment with simvastatin was withdrawn and on review six weeks later muscle cramps and weakness had improved although he still had the symptoms and signs of peripheral neuropathy. The CK

Institute of Clinical
Neurosciences, Royal
Prince Alfred Hospital
and University of
Sydney, Australia

T Phan
J G McLeod
J D Pollard

Department of
Neurology, Concord
Hospital, Sydney,
Australia
O Peiris

Adverse Drugs
Reaction Section,
Therapeutic Goods
Administration,
Woden, ACT 2600,
Australia
A Rohan

Department of
Neurology, Westmead
Hospital, Sydney,
Australia
J-P Halpern

Correspondence to:
Professor J G McLeod,
Department of Medicine,
University of Sydney, NSW
2006, Australia.

Received 16 August 1994
and in revised form
30 November 1994

Accepted 9 December 1994

Table 1 Motor conduction studies

Case	Time (months)	Median			Ulnar			Common peroneal			Post-tibial		
		Amplitude (mV)	Latency (ms)	CV (m/s)	Amplitude (mV)	Latency (ms)	CV (m/s)	Amplitude (mV)	Latency (ms)	CV (m/s)	Amplitude (mV)	Latency (ms)	CV (m/s)
1	0	7.1	3.8	56	6.2	3.6	57	1.8	4.9	41			
	7	7.5	3.6	46	2.6	3.1	59	0.9	4.9	42			
	18	7.1	3.7	53	4.9	2.4	55	1.7	4.4	43			
2	0	0.1	4.8	41	4.5	3.6	65	0.5	5.3	41	1.5	6.3	43
	12	0.1	7.1	21	4.0	3.2	54	0.1	5.3	50	1.3	5.5	37
3	0	4.3	3.6	48	3.9	2.8	56	1.2	5.2	41			
	1	6.2	4.6	46	4.0	2.3	48						
4	11	3.8	3.2	53	6.1	2.0	50						
	0										7.4	4.2	44
	3										5.3	4.4	44

concentration had fallen to 629 U/l. Electromyography in the lower limbs showed fasciculation potentials and large amplitude units firing in relative isolation. Spontaneous fibrillation was not recorded. Motor conduction velocities were in the normal range but sensory conduction was impaired.

Nine months after the withdrawal of simvastatin his symptoms had improved. There were fasciculations in the tongue and shoulder girdle and thigh muscles; there was mild distal weakness, ankle jerks could not be elicited, and painful sensation was mildly impaired on the feet. Other modalities of sensation were intact. Serum CK had fallen to 332 U/l. Motor conduction velocities were within the normal range but sensory conduction was impaired (tables 1 and 2). On last review, 18 months after withdrawal of simvastatin, there had been further clinical improvement although CK was still raised at 604 U/l; sensory conduction remained impaired (table 2).

CASE 2

A woman aged 66 presented with weakness of the lower limbs and difficulty in rising from a chair. After three months she was severely incapacitated and confined to a wheelchair; by four months she was unable to feed herself or to comb her hair and was admitted to a nursing home. She had pain in the fingers, the anterior aspects of the legs, and the lower thorax and abdominal wall but there was no complaint of numbness or tingling.

Treatment for hyperlipidaemia had started two years previously with simvastatin (10 mg daily) and the dose had been increased gradually to 40 mg daily one year before presentation. She was also receiving ranitidine (150 mg twice daily), digoxin (0.25 mg daily), aspirin (150 mg daily), and allopurinol (300 mg daily).

Neurological examination showed mild distal weakness in the upper limbs and asymmetric weakness and wasting of the lower limbs, particularly involving the left thigh, and profound proximal weakness. Reflexes were absent and sensation was normal. Five months later the patient was severely weak and wheelchair bound. Upper and lower limb muscles were wasted, most pronounced distally. Light touch and pain sensation were impaired in the upper limbs to the level of the wrists and in the lower limbs to the level of the ankles. Position sense was impaired at the fingers and toes and vibration sense was impaired to the level of the anterior superior iliac crests and wrists. Motor conduction velocities were mildly slowed in upper and lower limbs with reduced muscle compound action potential amplitudes (table 1) and sensory conduction was impaired (table 2). Electromyography showed widespread chronic partial denervation. Morphometric studies of sural nerve biopsy showed reduced density of large and small myelinated fibres (total density 4412 fibres/mm²; control range 6435–12544 fibres/mm²) with evidence of active axonal degeneration.

Haemoglobin, white cell count, erythrocyte sedimentation rate, serum electrolytes, liver function tests, serum proteins, blood glucose, urinary porphyrins, vitamins B1, B12, and E, C reactive protein, antineuronal, antinuclear, and anti-GM1 antibodies, urinary heavy metals, urinary porphyrins, and screening tests for vasculitis and collagen disorders were all normal. One month later, treatment with simvastatin was stopped; improvement followed and when re-examined nine months later she could feed herself, comb her hair, and walk with the aid of a stick. Power in all muscle groups in the upper and lower limbs had increased greatly since the previous

Table 2 Sensory conduction studies

Case	Time (months)	Median			Ulnar			Sural		
		Amplitude (μ V)	Latency (ms)	CV (m/s)	Amplitude (μ V)	Latency (ms)	CV (m/s)	Amplitude (μ V)	Latency (ms)	CV (m/s)
1	0	0	—	—	0	—	—	4.2	2.4	—
	7	2.0	2.5	—	0	—	—	0	—	—
	18	1.2	2.5	—	0	—	—	0	—	—
2	0	—	—	0	0	—	—	3.0	2.9	40
	12	0	—	0	0	—	—	0	—	—
3	0	2.0	2.7	46	5.0	2.4	47	3.0	3.3	37
	1	—	—	—	—	—	—	2.9	3.0	38
4	11	3.8	3.2	53	6.1	2.0	50	0	—	—
	0							6.5	3.0	31
	3							8.4	2.1	52

examination and sensation had returned to normal except for impairment of vibration sense at the ankles. No appreciable improvement had occurred in motor or sensory conduction after 12 months (tables 1 and 2).

CASE 3

A woman aged 65 presented for investigation of a four week history of upper and lower limb weakness. She had a history of hypertension for which she had been prescribed indapamide hemihydrate (2.5 mg daily), enalapril (20 mg daily), and pindolol (5 mg daily). She was otherwise in good health and played tennis regularly. Treatment with simvastatin had been commenced two years previously at a dose of 10 mg a day for hypercholesterolaemia and had been increased to 20 mg a day one year later. There was no relevant history. Four weeks before her presentation she developed an upper respiratory tract infection that was treated with erythromycin. At the same time she noticed the onset of weakness in her arms and legs. Initially she had difficulty in rising out of chairs and climbing stairs and weakness progressed over a period of six weeks until she was unable to lift her arms above her head, rise from a chair unaided, or walk without support. She complained of a burning sensation on the dorsum of the left foot.

On examination there was considerable generalised weakness in both her upper and lower limbs and truncal weakness. There was no muscle wasting or tenderness; reflexes were all present although ankle jerks were depressed. Vibration sense was absent to the level of the costal margin. A clinical diagnosis of polymyositis was suspected. Haemoglobin, white cell count, serum electrolytes, liver function tests, erythrocyte sedimentation rate and C reactive protein, serology for HIV and hepatitis B, rheumatoid antinuclear antibodies and extractable nuclear antigen, serum and urinary electrophoresis, tests for cryoglobulins, serum vitamin B12 concentrations, and thyroid function tests were all normal or negative. Serum CK was increased at 246 U/l. Protein in CSF was 0.4 g/l and there were no other abnormalities. A chest radiograph and CT myelogram showed no significant abnormalities. Electromyography showed evidence of acute denervation in upper and lower limb muscles, with the proximal muscles most severely affected. There were multiform fasciculations in all muscles sampled. Nerve conduction studies showed mild slowing of motor conduction velocities without conduction block and impairment of sensory conduction (tables 1 and 2). Muscle biopsy showed atrophic angular type 1 and 2 fibres with occasional fibres undergoing focal necrosis. Simvastatin treatment was withdrawn and four months later she had completely recovered clinically but nerve conduction studies showed no appreciable change (tables 1 and 2).

CASE 4

A woman aged 39 with primary hypercholes-

terolaemia was started on treatment with simvastatin (10 mg daily), after unsuccessful dietary management. Relevant history included an allergic diathesis with recurrent attacks of urticaria-angioedema, perennial allergic rhinitis, exercise induced asthma, and immediate hypersensitivity to salicylates and tetracyclines. She did not smoke tobacco or drink alcohol.

Within 24 hours of starting the drug she developed pain in her right calf, and later pain in her right groin and pains down both arms. These symptoms were followed by the development of a sensation of pins and needles in her fingertips and later the toes. There were no symptoms of muscle weakness or tenderness. There were no abnormalities on neurological examination; in particular, muscle tone, reflexes, and sensory examination were normal. Routine haematology and biochemistry investigations were unremarkable and serum CK was not raised (48 U/l). There were no abnormalities on electromyography. Motor conduction velocities were towards the lower limit of the normal range and sensory conduction was impaired (tables 1 and 2). An initial diagnosis of painful myopathy and predominantly sensory neuropathy was made. The simvastatin was discontinued after a total dose of 180 mg. There were no clinical or laboratory findings to suggest another cause of her neuropathy. On review three months later, the patient reported almost complete resolution of her symptoms except for the persistence of a few patches of hyperaesthesia over her body. Nerve conduction studies showed improvement in sensory conduction (table 2).

Discussion

These four patients presented with peripheral neuropathy associated with simvastatin treatment. The clinical presentation was with sensory and motor symptoms in case 1, muscle weakness with minor sensory symptoms in cases 2 and 3, and sensory symptoms in case 4. Proximal as well as distal muscle weakness were features in three patients, and two had muscle fasciculations. In three patients the finding of proximal and distal weakness and EMG evidence of widespread chronic partial denervation suggested the possibility of motor neuron disease. In all cases, however, a mixed sensorimotor neuropathy was found on electrophysiological studies. In two of the patients (cases 1 and 4) the onset of symptoms was soon after commencement of simvastatin treatment whereas in the other two (cases 2 and 3) onset was after an interval of two years. Improvement of the neuromuscular symptoms occurred after withdrawal of drug treatment; two patients (cases 3 and 4) reported almost complete resolution of symptoms after four months. In the other cases (cases 1 and 2) improvement was continuing after 15–18 months and there was still considerable residual disability. Because of the close relation of the onset of the peripheral neuropathy and muscle weakness to simvastatin

treatment and improvement after its withdrawal, together with the absence of any other cause, it is proposed that peripheral neuropathy in these cases was caused by simvastatin. Cases 1 and 2 may be considered as probable cases of simvastatin neuropathy, and cases 3 and 4 as possible cases. Electrophysiological studies suggested that the underlying pathology was most likely axonal degeneration as there were no features of demyelination and there was electromyographic evidence of denervation and this was confirmed on sural nerve biopsy in case 2. The prominent proximal and distal weakness and incomplete recovery of nerve conduction raise the possibility of a neuronopathy.

The Adverse Drug Reactions Advisory Committee (ADRAC) of Australia reported 22 cases of paraesthesiae and neuropathy associated with simvastatin.⁷ An updated search of the Australian database of suspected adverse drug reactions to the end of 1993 has increased this total to 38 cases, not including the four cases here. Sensory disturbances included "pins and needles", tingling, burning, numbness, or even frank muscle or joint pain. These symptoms were experienced most often in the limbs and extremities, but other locations such as the face, tongue, and scalp were also affected in some patients. Effects on motor function, which accompanied the sensory symptoms in some patients, included generalised weakness or localised paresis, often associated with myalgia; in one report, muscle atrophy was also noted. Recovery from the adverse reaction occurred in 22 cases, usually after merely stopping drug treatment. Five patients described a recurrence of the adverse reaction on re-exposure to the drug. In one patient, the reaction abated when simvastatin was taken as a morning dose; 11 patients had not fully recovered at the time the reports were submitted, and the outcome was not known in five patients.

A possible mechanism by which simvastatin could damage peripheral nerves is

through its action of mitochondrial function. It is a potent inhibitor of HMG-CoA reductase and not only blocks the synthesis of cholesterol but also that of dolichol and ubiquinone. Ubiquinone is a key enzyme in the mitochondrial respiratory chain and an intracellular deficiency of ubiquinone has the potential to disturb energy utilisation of the neuron. Mitochondrial dysfunction has also been postulated as the cause of the muscle weakness associated with HMG-CoA reductase inhibitors.^{5,8} Mitochondrial abnormalities have been reported in muscle biopsies of patients treated with simvastatin who developed progressive muscle pain and weakness and raised serum CK concentrations⁵; it was suggested that these patients had a subclinical mitochondrial myopathy that became expressed with an intracellular deprivation of ubiquinone after treatment. An isolated case has been reported in which treatment with ubiquinone (30 mg daily) was associated with clinical and biochemical improvement in a patient who had developed a myopathy when treated with lovastatin.⁸ Simvastatin is a widely used drug and should be considered among the causes of peripheral neuropathy. Treatment should be stopped in patients receiving simvastatin who develop muscle weakness and sensory disturbances.

- 1 Mabuchi H, Haba T, Tatami R, *et al.* Effects of an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme-A reductase on serum lipoproteins and ubiquinone-10 levels in patients with familial hypercholesterolemia. *N Engl J Med* 1981;305:478-82.
- 2 Boccuzzi SJ, Bocanegro TS, Walker FJ, Shapiro DR, Keegan ME. Long-term safety and efficacy profile of simvastatin. *Am J Cardiol* 1991;68:1127-31.
- 3 Walker FJ. Simvastatin: the clinical profile. *Am J Med* 1989;87:44S-46S.
- 4 Stalenhoef AFH, Mol MJTM, Stuyt PMJ. Efficacy and tolerability of simvastatin (MK-733). *Am J Med* 1989; 87:39S-43S.
- 5 England JD, Viles A, Walsh JC, Stewart PM. Muscle side effects associated with simvastatin therapy. *Med J Aust* 1990;153:562-3.
- 6 Bizzaro N, Bagolin E, Milani L, Cereser C, Finco B. Massive rhabdomyolysis and simvastatin. *Clin Chem* 1992;38:1504.
- 7 ADRAC. Paraesthesia and neuropathy with hypolipidaemic agents. *Australian Adverse Drug Reactions Bulletin* 1993;12:6.
- 8 Walravens PA, Greene C, Frerman FE. Lovastatin, isoprenes and myopathy. *Lancet* 1989;ii:1097-8.



Peripheral neuropathy associated with simvastatin.

T Phan, J G McLeod, J D Pollard, O Peiris, A Rohan and J P Halpern

J Neurol Neurosurg Psychiatry 1995 58: 625-628

doi: 10.1136/jnnp.58.5.625

Updated information and services can be found at:
<http://jnnp.bmj.com/content/58/5/625>

Email alerting service

These include:

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>