Lessons from practice

Pregabalin-associated rhabdomyolysis

Roshan Gunathilake
MB BS, MD,
Advanced Trainee[1]

Laura E Boyce
BPharm,
Pharmacist[2]

Anne T Knight
MB BS(Hons), FRACP,
General Physician[2]

1 Department of Medicine,
John Hunter Hospital,
Newcastle, NSW.

2 Manning Rural
Referral Hospital,
Taree, NSW.

roshangun@yahoo.com

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Clinical record

A 66-year-old white Australian woman presented to the emergency department in May 2013 with a suspected ankle fracture after a fall. She had developed rapid onset of severe myalgia and muscle weakness 3 days earlier, leading to gait instability. There was no history of prolonged immobilisation after the fall. Her renal function had previously been normal. Two days before the onset of muscular symptoms, she had commenced taking pregabalin 75 mg twice daily for trigeminal neuralgia. She had been taking atorvastatin 40 mg daily for hyperlipidaemia for 5 years without any adverse effects. Her medical background also included treated hypertension, stable chronic heart failure, obstructive sleep apnoea, chronic back pain, and depression. There had been no recent changes to her regular medications, which included aspirin, irbesartan, frusemide, spironolactone, sodium valproate, venlafaxine, oxycodone, paracetamol and a budesonide–eformoterol turbuhaler.

On examination, she had proximal weakness in the upper and lower limbs (Medical Research Council scale 4/5), with diffuse muscle tenderness, but no other focal neurological signs. There was oedema and tenderness over the left ankle due to fractures of the distal tibia and fibula, and lateral dislocation of the talus, confirmed by radiography. Lower limb neurovascular function was intact, and no other injuries were found. The rest of the clinical examination was unremarkable. She was oliguric on admission but responded promptly to intravenous fluid challenge. Urinalysis was consistent with myoglobinuria. Results of laboratory investigations showed evidence of skeletal muscle damage, acute kidney injury and neutrophil leukocytosis (Table). She had an international normalised ratio of 1.0. Thyroid function and autoimmune screening tests did not show any abnormality.

Rhabdomyolysis was diagnosed on clinical and biochemical grounds, and pregabalin and atorvastatin were ceased. Diuretics and irbesartan were withheld in the setting of acute kidney injury. Aggressive fluid resuscitation was continued. Her renal function returned to normal within 48 hours, the creatine phosphokinase level gradually returned to normal over 7–8 days, and her muscle strength improved. She underwent open reduction and internal fixation of her fractured ankle on Day 4, and was referred for inpatient rehabilitation a week after hospital admission. ◆

Laboratory test	Level	Reference interval
Creatine phosphokinase	14 050 U/L	29–168 U/L
Aspartate transaminase	441 U/L	5–34 U/L
Alanine transaminase	138 U/L	< 55 U/L
Serum creatinine	178 μmol/L	50–98 μmol/L
eGFR	27 mL/min/1.73 m^2	> 60 mL/min/1.73 m^2
White blood cell count	23.6 × 10^9/L	4–12 × 10^9/L
Neutrophils	19.8 × 10^9/L	1.8–7.7 × 10^9/L
Haemoglobin	126 g/L	115–160 g/L
Platelet count	193 × 10^9/L	150–400 × 10^9/L
Serum sodium	134 mmol/L	136–145 mmol/L
Serum potassium	5.2 mmol/L	3.5–5.1 mmol/L
Serum ionised calcium	1.11 mmol/L	1.04–1.24 mmol/L
Phosphate	1.95 mmol/L	0.74–1.52 mmol/L
Bilirubin	11 μmol/L	3–21 μmol/L
Alkaline phosphatase	56 U/L	35–104 U/L
γ-Glutamyl transferase	97 U/L	9–36 U/L
Albumin	33 g/L	35–50 g/L

eGFR = estimated glomerular filtration rate.

Pregabalin is a γ-aminobutyric acid (GABA) analogue that binds to the α2-δ subunit of voltage-gated calcium channels in the central nervous system. It is approved for treating neuropathic pain and partial epilepsy.[1] Pregabalin was listed on the Pharmaceutical Benefits Scheme in March 2013 as Australia's first drug to be subsidised specifically for neuropathic pain.

Pregabalin shows linear pharmacokinetics and a predictable dose–response relationship.[2] It is rapidly absorbed in the fasting state, with 90% oral bioavailability. Steady-state plasma concentration is obtained in 24–48 hours. It does not bind to plasma proteins and more than 98% is excreted unchanged in urine; the elimination half-life is 6 hours but is dependent on creatinine clearance.[2] Dose reduction is therefore needed in patients with impaired renal function.

There were three premarketing reports of severe rhabdomyolysis associated with pregabalin.[1] In controlled trials, 1.5% of patients taking pregabalin and 0.7% of patients taking placebo had creatine phosphokinase levels at least three times the upper limit of normal.[1] We searched the Therapeutic Goods Administration database of adverse event notifications for "pregabalin and rhabdomyolysis" and found one report each of rhabdomyolysis and myopathy, with pregabalin the only suspect drug in both cases, plus 12 reports of muscular weakness and eight of myalgia.[3] In only one case was the patient reported to be taking a statin. Statins are well known to cause myositis and rhabdomyolysis. It is not known whether the combination of pregabalin and a statin synergistically increases the risk of myositis. In a reported case of severe rhabdomyolysis in a patient receiving simvastatin and pregabalin, interference with the renal elimination of hydrophilic metabolites of simvastatin was proposed as a possible site of drug interaction.[4] Statins that are cytochrome-dependent for metabolism, such as simvastatin and, to a lesser extent, atorvastatin, are likely to be involved in drug interactions and cause statin-induced myopathy when used concomitantly with drugs that interfere with the CYP3A4 isoenzyme.[5] However, pregabalin undergoes negligible hepatic metabolism and does not induce or inhibit the cytochrome P450 system.[2]

Two other case reports have described rhabdomyolysis in patients taking myotoxic medications in addition to pregabalin: a case of fatal rhabdomyolysis in a patient who had recently started taking atorvastatin and fusidic acid as well

as pregabalin;[6] and a patient with gemfibrozil-induced myositis, who developed rhabdomyolysis after starting pregabalin.[7] We applied the Naranjo probability scale[8] to these two cases[6,7] and found a possible association (score, 1–4) between pregabalin and the rhabdomyolysis.

Our patient had been taking a statin at a stable dose for many years without myositis. Severe rhabdomyolysis in this case resulted from pregabalin and possibly atorvastatin. The Naranjo scale indicates a probable adverse drug reaction (score, 5–8) due to pregabalin. Prerenal renal failure secondary to decreased oral intake during the initial phase of her acute illness could have contributed to pregabalin- and/or statin-induced myositis.

Patients who commence pregabalin should be advised to report unexplained muscle pain, tenderness or weakness. Pregabalin should be discontinued if myopathy is suspected or diagnosed. Physicians prescribing pregabalin to patients who are taking other potentially myotoxic drugs, such as statins, should be aware of reports of adverse reactions.

Lesson from practice

- Clinicians should be aware of the rare occurrence of pregabalin-associated rhabdomyolysis and exercise caution in coprescribing pregabalin with other potentially myotoxic drugs. ◆

Competing interests: No relevant disclosures.

1 Pfizer Australia. Product information: Lyrica (pregabalin). Canberra: Therapeutic Goods Administration, 2013. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04219-3 (accessed May 2013).

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