CASE REPORT

Seizure induced by sudden cessation of pregabalin in a patient with chronic kidney disease

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SUMMARY

A middle-aged woman with diabetic nephropathy on pregabalin for neuropathic pain presented with a diarrhoeal illness. She was found to have acute on chronic renal impairment with an estimated glomerular filtration rate (eGFR) of 10 mL/min, and her usual 150 mg/day of pregabalin was abruptly ceased. Although renal recovery to her baseline of eGFR 15 mL/min was achieved within 3 days, her pregabalin was not restarted. She suffered a tonic–clonic seizure 4 days later, thought to be due to pregabalin withdrawal as there were no other likely causes identified. She suffered no further seizures on recommencement of pregabalin at a renally adjusted dose of 75 mg/day.

BACKGROUND

This is a novel case where a middle-aged woman with diabetes with neuropathic pain suffered a pregabalin withdrawal seizure after abrupt cessation of this medication in the setting of acute on chronic renal impairment.

Pregabalin is a widely prescribed drug in Australian hospital and community settings for both neuropathic pain and as adjunctive therapy in focal seizures. However, there are no reports to indicate that suddenly stopping pregabalin in patients using it for management of neuropathic pain could precipitate a seizure, even in those with no known propensity. Our case highlights the important clinical message of the need for caution when ceasing pregabalin or adjusting doses, even when it is not used as an antiepileptic. Our case may have been particularly predisposed through the use of higher than usual doses of pregabalin and accumulation of drug due to renal impairment prior to its sudden discontinuation. This article will be of interest to the wide readership audience of *BMJ* Case Reports from general practice through to specialist care.

CASE PRESENTATION

A 52-year-old Caucasian woman presented to the emergency department with diarrhoea and abdominal pain for 2 days. She had a 3-month history of progressive decline in urine output, with a 3-week history of increasing malaise, lethargy, somnolence, nausea, decreased appetite and low blood pressure (BP). She had been on pregabalin for many years to manage diabetic neuropathy pain in her back, neck and limbs, and was taking 50 mg mane and 100 mg nocte on admission. She had long-standing type 1 diabetes mellitus with multiple complications, including retinopathy, peripheral and autonomic neuropathy, and stage 4 chronic kidney disease. Her medical history is also significant for hypothyroidism, glucose-6-phosphate dehydrogenase deficiency and osteoporosis with prior stress fracture. She had no family history of epilepsy and only ever had one seizure 5 years ago in the setting of profound hypoglycaemia. She is a reformed smoker with 25 pack years. Her other medications include continuous subcutaneous NovoRapid insulin, ramipril, rosuvastatin, darbepoetin alfa, thyroxine, calcium carbonate, cephalexin, fish oil and glucosamine.

On examination, she was clinically dehydrated with mild hypotension that was fluid-responsive. The cardiorespiratory and abdominal examinations were unremarkable. A normal anion gap metabolic acidosis and an acutely elevated serum urea of 25 mmoL/L (reference range (RR) 2.7–8.0 mmoL/L) and creatinine of 400 μmoL/L (baseline 280 μmoL/L, RR 50–100 μmoL/L) were detected. She was diagnosed with prerenal failure from dehydration and treated with intravenous fluids and an insulin infusion. Her pregabalin was stopped in view of her estimated glomerular filtration rate (eGFR) of 10 mL/min/1.73 m^2.

She had no further diarrhoea after admission and deemed to have had viral gastroenteritis. Rapid renal recovery was achieved with her creatinine returning to baseline at 280 μmoL/L by day 3 of admission. However, she remained nauseous and her anorexia persisted.

On day 4 of her admission, she was found slumped on the bathroom floor complaining of feeling strange and dizzy. She was returned to bed where she was found to be acutely hypertensive (BP 190/110) and became unresponsive. She was then observed to have jerking movements of all four limbs and roving generalised eye movements typical of a generalised tonic–clonic seizure. Urgent bloods were taken which showed glucose of 17.6 mmoL/L, Na 142 mmoL/L, K 4.0 mmoL/L and creatinine of 280 μmoL/L. The jerking movements ceased after 5 min, and she became alert, responsive and oriented over the next hour. Neurological examination was unremarkable other than transient upgoing plantar responses. She was given a loading dose of sodium valproate intravenously and sent for urgent CT head, which did not show any abnormality.

Pregabalin withdrawal seizure was diagnosed on clinical grounds, and her pregabalin was restarted at 25 mg mane and 50 mg nocte (maximum recommended dosage for her GFR of 14 mL/min/1.73 m^2).

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She suffered no further seizures and felt that her nausea was improved. She remained well and was discharged home on day 7 of her admission.

DISCUSSION

Pregabalin is widely used as treatment of neuropathic pain in adults with evidence of diabetic peripheral neuropathy.[1] It is also indicated for adjunctive therapy in adults with partial seizures with or without secondary generalisation.[2] In the first 12 months of pregabalin listing on the Pharmaceutical Benefits Scheme (PBS) for neuropathic pain, a total of 294 274 patients were given over 1.3 million prescriptions between March 2013 and March 2014.[3]

Its exact mechanism of action is unknown, although it is understood that it works by binding to alpha-2 delta protein subunit of high threshold voltage-dependent calcium channels, reducing calcium influx.[4] In addition, pregabalin reduces the synaptic release of several neurotransmitters through this binding, including glutamate, noradrenaline and substance P, possibly explaining its actions in vivo, reducing neuronal excitability and seizures.[5] Elimination of the drug is primarily through renal excretion, and dose reduction is recommended in renal impairment.

Although the adverse and toxic effects of pregabalin are relatively well known, withdrawal effects are less appreciated. Withdrawal symptoms of pregabalin have been reported to include insomnia, headache, nausea, anxiety, diarrhoea, dizziness, nervousness and spasticity.[6–8] However, a search of the current literature has not yielded any reports of seizures as a result of pregabalin withdrawal.

Our patient did not have any personal or family history of epilepsy, and the only other seizure she experienced was in the context of severe hypoglycaemia 5 years ago. Her pregabalin was stopped on admission due to her acute on chronic kidney impairment with an eGFR of 10 mL/min/1.73 m^2. Although her renal function recovered to baseline by day 3 of her admission with eGFR improved to 15 mL/min/1.73 m^2, the drug was not recommenced. At the time of her seizure on day 4 of admission, there was no electrolyte or metabolic derangement, hypoglycaemia or intracranial abnormalities that could be implicated.

We postulated two factors that could have contributed to the seizure in this woman. First, it is likely she had supratherapeutic levels of pregabalin on admission given her acute on chronic renal impairment. Given her eGFR of 10 mL/min/1.73 m^2 on admission, the maximum recommended daily pregabalin dose was 75 mg — she had been on double this dose. This could potentially also account for her symptoms of lethargy, somnolence and low blood pressure for the weeks prior to her admission. Second, the abrupt cessation of pregabalin may have led to a relative overdischarge of neurotransmitters in the central nervous system, which would usually be under tonic inhibition from the actions of pregabalin. Accumulation of pregabalin due to renal impairment prior to its cessation may have accentuated the rate of drug disappearance following withdrawal, exacerbating neuronal excitability. This culminated in a tonic–clonic seizure 4 days later in a patient with no obvious underlying predisposition to seizures.

As a result of her seizure, this patient had to suffer a 6-month driving ban, which greatly inconvenienced her and negatively impacted her quality of life. This is an iatrogenic complication that could have been avoided with appropriate medication tapering and dose adjustment. We hope this case highlights the potential dangers of sudden pregabalin cessation even when not used for its antiepileptic properties.

Learning points

- We recommend regular monitoring of renal function in all patients on pregabalin, with dosage adjustment as necessary.
- We recommend caution when ceasing or adjusting doses of pregabalin, especially in the presence of severe renal impairment.
- We recommend gradually withdrawing pregabalin over a minimum of 1 week if it were to be discontinued, in accordance with current recommended practice.

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