Pregabalin and paradoxical reaction of seizures in a large overdose

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ABSTRACT

We report the case of a 54-year-old female with intentional pregabalin 3825 mg ingestion that resulted in a rare adverse effect of a witnessed seizure with confirmatory serum concentrations. After presenting alert to the emergency department she became obtunded, only responding to sternal rub (four hours after ingestion). Laboratory evaluation and toxicology panel were unremarkable. Approximately eight hours after the ingestion she had physician-witnessed tonic–clonic seizure activity with right gaze deviation for 90 seconds. This is only the third documented case of paradoxical seizure due to a large overdose of pregabalin. Also, the serum concentration observed is among the highest recorded (58 mcg/mL five hours post-ingestion). Pregabalin abuse has been emerging. Clinical toxicologists should be aware of the potential of pregabalin-induced seizures following overdose.

Pregabalin (Lyrica®, Pfizer) is a γ-aminobutyric acid analogue that modulates calcium influx at nerve terminals inhibiting excitatory neurotransmitter release. Toxicity may occur after overdose or at therapeutic doses following accumulation in the setting of renal impairment. Expected toxicity is central nervous system (CNS) depression. We report a case of intentional pregabalin overdose resulting in a rare adverse effect of seizure with confirmatory serum concentrations.

A 54-year-old female with chronic back pain and substance use disorder presented to the emergency department (ED) complaining of “spasms” three hours after taking a large amount of pregabalin (3825 mg). She denied co-ingestants but had access to atenolol, cyclobenzaprine, and quetiapine as her home medications. On presentation, vital signs were blood pressure 156/110 mmHg, heart rate 111 beats/minute, temperature 37.3 °C, respirations 24 breaths/minute, and oxygen saturation 100% on room air. She was initially alert but became obtunded approximately one hour after ED presentation, responding only to sternal rub. At the time the patient became obtunded vital signs were blood pressure 131/74 mmHg, heart rate 93 beats/minute, respirations 16 breaths/minute, and oxygen saturation 100% on nasal cannula. Laboratory evaluation (including electrolytes, liver function tests) and toxicology panel (acetaminophen, salicylate, alcohol) were unremarkable (serum creatinine 0.63 mg/dL). An electrocardiogram showed sinus tachycardia. On examination, she was lethargic with rotary nystagmus and myoclonic jerks. Approximately eight hours after ingestion she had physician-witnessed tonic–clonic seizure activity with right gaze deviation, and involuntary movements of the mouth that lasted 90 seconds. She was also foaming at the mouth, tachycardic (140 beats-minute), hypertensive (170/120 mmHg), and had oxygen desaturation (90% while on 2 L/minute nasal cannula). The seizure was self-limited. She received a single dose of lorazepam 0.5 mg IV immediately following. Upon resolution, she returned to an obtunded state, was responsive to pain, and maintained her airway. Baseline mental status returned 13 hours after ingestion. Pregabalin concentration five hours after ingestion was 58 mcg/mL (patient would open eyes to voice, grunt, fidget in bed, but not respond verbally at this time). Chronic daily doses of 150 and 600 mg/day result in steady-state concentrations averaging 1.3 and 4.9 mcg/mL, respectively [1].

Although CNS depression typifies pregabalin overdose, myoclonus may also occur. However, to our knowledge, this is only the third published case of seizure associated with an intentional pregabalin overdose [2]. A previous brief case series of two friends, 16- and 17-year-old males, who were both otherwise healthy developed generalized seizures after intentionally...
ingested as much as 2700 mg and an unknown amount of pregabalin, respectively. Only the second patient had a witnessed generalized tonic–clonic seizure by a health care provider. Co-ingestants were unclear despite extended urine drug screen being negative for the first patient and positive for tetrahydrocannabinol for the other. The patient who ingested up to 2700 mg had a plasma pregabalin concentration of 27 mcg/mL while the second patient (unknown quantity ingested) had a plasma pregabalin concentration of 43 mcg/mL [2]. The timing of these concentrations was not discussed. It is curious that both patients experienced this previously undocumented paradoxical reaction to pregabalin simultaneously. Two additional reports describe three patients experiencing seizures while using therapeutic pregabalin for complex-partial seizures or chronic neuropathy (dose 150–300 mg daily) [3,4]. One patient with previous seizure disorder experienced worsening seizures and new seizure patterns, cognitive impairment and incontinence [3]. Two patients without prior seizure disorder had a mild increase in serum creatinine (1.23 and 1.48 mg/dL) and experienced lethargy, myoclonic jerks, and seizures confirmed on electroencephalography (EEG) [4]. All individuals had improved symptoms, EEG normalization, and return to baseline following pregabalin discontinuation. Our patient had similar symptoms to others without previous seizure disorders with complete resolution following discontinuation of pregabalin.

The remaining reported cases of pregabalin-induced myoclonus have been in the setting of renal impairment [5,6]. Being that pregabalin is eliminated almost completely by the kidneys, any impairment can increase the risk of toxicity, even at therapeutic doses. One case reported a 67-year-old female with diabetic nephropathy who was taking 600 mg, divided three times daily, for ongoing radicular leg pain post laminectomy. Within 24 hours of starting pregabalin, the patient started to experience dizziness, twitching of all limbs, diplopia, confusion, and ataxia. Laboratory values were only significant for a creatinine of 1.78 mg/dL. The patient was ultimately admitted for delirium and inability to ambulate and returned to baseline within 48 hours after cessation of pregabalin [5]. The second reported case was in a 30-year-old female who had been on hemodialysis therapy for several years due to obstructive uropathy. The patient was on pregabalin 50 mg per day for neuropathic hand pain and was rapidly increased to 225 mg, divided three times daily. By hospital day 5, she reported uncontrollable contractions of the face and arms, without alteration in mental status. Interestingly, after the 225 mg per day ingestion, the patient’s predialysis serum was 13 mcg/mL, the same concentration at which she experienced myoclonus [6].

Our patient’s serum concentration is among the highest reported. A previous case report identified a concentration of 66.5 mcg/mL (three hours post-ingestion of pregabalin 8.4 g) [7]. A separate report identified a concentration of 29 mcg/mL (9 hours post-ingestion of an unknown quantity of pregabalin) [8]. Both patients experienced CNS depression without seizures. Pregabalin abuse has been emerging, especially among opioid abuse patients [9]. Current efforts to curtail prescription opioid use may lead to increase use of pregabalin and gabapentin for chronic pain. Clinical toxicologists should be aware of the potential for seizures following pregabalin overdose.

Disclosure statement
All authors have nothing to disclose.

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