Significant Pregabalin Toxicity Managed with Supportive Care Alone

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Abstract There are two previously reported cases describing the management of pregabalin self-poisoning and one further case of management of therapeutic pregabalin accumulation. The peak reported pregabalin concentrations in these cases ranged from 13 mg/L to approximately 60 mg/L. Previous case reports have suggested that both supportive care and enhanced elimination are appropriate managements for pregabalin toxicity. A 54-year-old male presented following ingestion of 8.4 g of pregabalin. Initially, he had no clinical features of toxicity, although he developed significant neurological depression and coma approximately 3 h post-ingestion. He was managed with supportive care (including endotracheal intubation and mechanical ventilation) until his level of consciousness improved. Subsequent toxicological screening confirmed isolated pregabalin ingestion, with a serum pregabalin concentration of 66.5 mg/L at the time he clinically

deteriorated. The pharmacokinetic properties of pregabalin indicate the potential value of extra-corporeal elimination methods such as haemodialysis. Clinical toxicologists should be aware that whilst there is a pharmacokinetic basis for the use of extra-corporeal methods in those with severe toxicity arising from excessive plasma pregabalin concentrations, there are case reports, including this one, where patients have been managed with supportive measures only.

Keywords Pregabalin · Toxicity · Overdose

Introduction

Pregabalin is a lipophilic analogue of γ -aminobutyric acid (GABA) and has a similar chemical structure to gabapentin. It is currently licensed for the treatment of neuropathic pain (in particular, diabetic peripheral neuropathy and post-herpetic neuralgia), generalised anxiety disorder and as a second line drug for the management of partial epilepsy. Unwanted clinical effects, including dizziness, somnolence, weight gain, psychosis and myoclonus, have been reported during therapeutic use of pregabalin at doses of 50 to 600 mg/day [1, 2].

There are two reported cases of toxicity associated with pregabalin self-poisoning [3, 4]. Both of these patients were managed conservatively, with airway and respiratory support required in only one of them, although this patient also had a lamotrigine concentration of approximately 45 mg/L [3]. In addition, there is one further reported case of pregabalin toxicity associated with therapeutic use resulting in pregabalin accumulation in a patient with chronic renal failure that was managed with haemodialysis [5]. Peak reported pregabalin concentrations in these

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patients ranged from 13 mg/L to approximately 60 mg/L [3–5]. Apart from these case reports, there is limited information available on the frequency of pregabalin self-poisoning. The American Association of Poison Control Centers annual reports do not include data on pregabalin, apart from when it is involved in a fatality [6]. In terms of pregabalin-associated fatalities in these annual reports, pregabalin was not mentioned in any fatalities prior 2006. Between 2006 and 2008, pregabalin has been listed as a drug used/ingested in approximately 1% of fatalities; none of these cases were isolated pregabalin cases [6].

We report here a case of isolated pregabalin toxicity with the highest recorded pregabalin concentrations to date that was successfully managed with conservative treatment only.

Case Report

A 54-year-old male, with a past medical history of human immunodeficiency virus (HIV) infection, HIV-related peripheral neuropathy and type 2 diabetes mellitus, presented to the Emergency Department (ED) after a self-reported ingestion of 8.4 g of pregabalin; he denied ingestion of any other drugs. On presentation to the ED, he was alert with a Glasgow Coma Score (GCS) of 15, cardiovascularly stable with a heart rate of 99 bpm and blood pressure of 127/60 mmHg, afebrile with a temperature of 37.0°C and had good respiratory effort with a respiratory rate of 20. Initial investigations showed normal renal function (sodium 140 mmol/L, potassium 4.6 mmol/L, creatinine 76 µmol/L and urea 7.0 mmol/L) and mild pre-existing liver dysfunction (alanine aminotransferase 61 IU/L, alkaline phosphatase 218 IU/L, bilirubin 5 µmol/L, gamma-GT 699 IU/L and albumin 40 g/L); paracetamol and salicylate were both undetectable on screening. As he was clinically stable on presentation, he had neither an electrocardiogram (ECG) nor arterial blood gases performed. He presented less than an hour after ingestion, and so, he was administered a single 50-g dose of activated charcoal and was observed in the ED for signs of clinical deterioration.

Approximately 3 h post-ingestion, he deteriorated, becoming unresponsive with a GCS of 4/15; it is unclear the time course over which his conscious level deteriorated as this was not observed. He remained cardiovascularly stable at this time with a heart rate of 99 bpm and blood pressure of 134/85 mmHg. His ECG showed borderline sinus tachycardia, but QRS (69 ms) and QTc (414 ms) durations were normal. There had been no witnessed seizures in the ED prior to this clinical deterioration, and therefore, it was felt unlikely that his clinical condition was a post-ictal phase. Due to his reduced conscious level, he was intubated for airway protection and mechanically

ventilated, prior to admission to the Intensive Care Unit (ICU) for ongoing supportive care. Clinical toxicology review was undertaken. While extra-corporeal methods may enhance elimination, in this case, it was decided that the patient should be managed with airway and general supportive care alone, anticipating spontaneous recovery.

He remained cardiovascularly stable, and his GCS improved over the next 24 h, enabling extubation 26 h after admission to ICU. His admission was complicated by aspiration pneumonia, which was treated with intravenous cefuroxime and metronidazole. Once the patient had improved clinically, he stated that he did not wish to remain in hospital for further treatment; a detailed psychiatric review was undertaken to ensure that he had both the capacity to leave and was not thought to have ongoing features of pregabalin toxicity. Following this, as he was deemed to have capacity and had no ongoing features of pregabalin toxicity, he signed out against medical advice.

Toxicological Screening

Informed consent was obtained from the patient prior to discharge for retrospective toxicological analysis of biological samples that had been collected for routine investigations. Pregabalin concentrations were measured in the plasma samples that had been obtained from the admission using a previously described method [7]. The pregabalin concentration, at the time the patient became comatose (approximately 3 h post-ingestion), was 66.5 mg/L. This had fallen to 51.2 and 15.2 mg/L, respectively, at approximately 7 and 27 h post-ingestion.

Comprehensive toxicological screening of urine by gas chromatography mass-spectrometry detected only cannabinoids in addition to drugs that he was taking therapeutically or had been given in the ED and ICU (atracurium, lidocaine, efavirenz and metronidazole).

Discussion

We have described here a case of severe toxicity following self-poisoning, with pregabalin alone. The serum pregabalin concentration, in this patient of 66.5 mg/L, is the highest yet reported, and he was managed with supportive treatment only. Very little information is available regarding therapeutic serum/plasma concentrations of pregabalin. However, one report states that in samples collected at random times relative to dose from patients maintained on 600 mg/day, plasma pregabalin concentrations ranged from 0.9 to 14.2 mg/L [8]. Pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations within an hour of dosing and up to 90% oral bioavailability [9]. There is little hepatic

metabolism of pregabalin, and over 90% of pregabalin elimination is through renal excretion of the non-metabolised pregabalin [9].

There have been two previous reported cases of pregabalin toxicity following deliberate self-poisoning [3, 4]. One patient presented with mild drowsiness following ingestion of an unknown amount of pregabalin and required supportive management only; this patient had a pregabalin concentration of 29 mg/L 9 h post-ingestion [4]. The other case was a patient who ingested 11.5 g of pregabalin, together with 32 g of lamotrigine, who initially developed abnormal facial and generalised body movements and drowsiness [3]. The ‘initial’ pregabalin plasma concentration was approximately 60 mg/L, but the sample also contained lamotrigine at a concentration of approximately 45 mg/L. Clinical effects of lamotrigine self-poisoning, at ingested doses of ≤ 22.5 g, include coma [10]. Furthermore, unwanted clinical effects, such as rash, nausea, vomiting and visual disturbances (blurred vision and diplopia), have been seen at mean lamotrigine concentrations above 15 mg/L in therapeutic use [11, 12]. It is therefore possible that some of the initial clinical symptoms in this patient were contributed to by the lamotrigine that had been ingested, instead of being due to solely the pregabalin ingested.

Pregabalin has a low volume of distribution (approximately 0.5 L/kg), low molecular weight (approximately 159 Da) and is not protein bound [9]. These pharmacokinetic features make it likely that elimination of pregabalin would be enhanced by the use of extra-corporeal methods such as haemodialysis and/or haemofiltration. A recently published case report describes an individual with haemodialysis-dependent end-stage renal failure who developed myoclonus, which was thought by the authors to relate to pregabalin accumulation following an increase in the prescribed dose [5]. Toxicity may have occurred due to the fact pregabalin is excreted unchanged by the kidneys, and there are recommendations for dose adjustment in patients with renal impairment/failure [9]. Pregabalin was discontinued, and the patient managed with an additional haemodialysis, resulting in improvement of the clinical symptoms.

The present case describes a patient with very high serum pregabalin concentrations who was managed with

supportive treatment only and made a full recovery. The pharmacokinetic properties of pregabalin indicate the potential value of extra-corporeal elimination methods such as haemodialysis. Clinical toxicologists should be aware that whilst there is a pharmacokinetic basis for the use of extra-corporeal methods in those with severe toxicity arising from excessive plasma pregabalin concentrations, there are case reports, including this one, where patients have been managed with supportive measures only.

Competing interests The authors report no declarations of interest.

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