

## CASE REPORT

# Coma after levetiracetam overdose

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Levetiracetam is an anticonvulsant prescribed for partial seizures and as an adjunct in the treatment of generalised tonic-clonic seizures. Adverse effects are relatively mild in comparison with older anticonvulsants. We present the case of a 50-year-old patient who ingested over 20,000 mg of levetiracetam in a suicide attempt. When she arrived at the emergency department nine hours after ingestion she was comatose and required intubation and ventilatory support for 24 hours. Thirty-six hours after admission she had completely recovered. Although the recent literature reports mostly mild symptoms even with very high ingested doses, this case shows that potentially life-threatening side effects can occur with lower doses than previously described and that psychiatric side effects are important. Moreover this case showed that life-threatening symptoms do not require high blood levels.

## Introduction

Levetiracetam was first introduced in 2000 as a new anticonvulsant prescribed for partial seizures and as an adjunct in the treatment of generalised tonic clonic seizures.<sup>1,2</sup> The exact mechanism of action is not fully elucidated but presumably levetiracetam influences the intraneuronal calcium concentration and the sensitivity for GABA and glycine channels. In general, levetiracetam is a potent and well-tolerated anticonvulsant used in the treatment of a broad range of seizure types. The most common side effects are drowsiness, headache, behavioural disturbances and nasopharyngitis.<sup>3</sup>

Levetiracetam has a favourable pharmacokinetic profile with rapid absorption following oral administration, excellent bioavailability, rapid achievement of steady-state concentrations, linear kinetics and minimal plasma protein binding. The maximal concentration (C<sub>max</sub>) is reached after 1.3 hours and the volume of distribution is 0.5-0.7 l/kg. Sixty-six percent of an administered dose is eliminated unchanged and 24% is excreted in urine as inactive metabolites after metabolism in the liver. Clearance is fairly rapid, with an elimination half-life of 6-8

hours and about 93% of the drug is excreted within 48 hours after oral administration. Levetiracetam metabolism is not dependent on the hepatic CYP.<sup>4</sup> The recommended dosing is to start with 1000 mg/day increasing stepwise to a maximum recommended dose of 3000 mg daily<sup>5</sup> and therapeutic serum concentrations are reported to be within the range of 5-25 µg/ml.<sup>3</sup> In patients with partial and/or generalised seizures levetiracetam initiated at doses of 2000 mg or 4000 mg daily is well-tolerated and effective as add-on therapy. However, the higher dose is not necessarily more effective and may be related to an increased incidence in somnolence.<sup>2</sup>

A recent observational study suggested that levetiracetam was the least toxic among the newer anticonvulsants such as gabapentin, lamotrigine and pregabalin.<sup>6</sup> Since clinicians may have limited experience with overdose due to newer anticonvulsants, reporting anecdotal cases is important in gaining insight regarding this subject. We aim to provide an illustration of the possible life-threatening events associated with ingestion of a high dose of levetiracetam. In addition we want to emphasise the importance of potential psychiatric side effects associated with this drug.

## Case description

A 50-year-old woman was brought to the emergency department because of impaired consciousness. Previous medical history revealed obesity (BMI 38 kg/m<sup>2</sup>) and an aneurysmal subarachnoid haemorrhage complicated by delayed cerebral ischaemia resulting in mild aphasia, a right-sided spastic hemiparesis and status epilepticus in 2007. The epilepsy was initially treated with phenytoin and later sodium valproate. Because of weight gain associated with sodium valproate use the anticonvulsant therapy was changed into levetiracetam in 2010. Over the last two years the patient repeatedly expressed suicidal thoughts to her husband and general practitioner. On the evening before admission she had three beers and when her husband found her vomiting and confused at night he

attributed these symptoms to the consumed alcohol. Because the patient became unresponsive and started to snore he called for an ambulance approximately 4 hours later. Upon arrival, the paramedics found a comatose patient with a Glasgow Coma Score of 3 and an obstructive breathing pattern. Brain stem reflexes were present. Vital parameters included an oxygen saturation of 85%, a regular heart rate of 77 beats per minute and a blood pressure of 172/103 mmHg.

The husband found empty blisters of levetiracetam, paracetamol and baclofen and an empty medication dispenser. An intentional overdose was considered and the estimated maximum ingested doses were 20,000 to 27,000 mg of levetiracetam, 4000 to 6000 mg of paracetamol and a maximum of 200 mg of baclofen. The patient was given supplemental oxygen and was transferred to the emergency department of our hospital. She was intubated, started on N-acetylcysteine because of the possible paracetamol ingestion and admitted to the intensive care unit. A head CT scan showed signs of the earlier coiling procedure and an old infarction in the arteria cerebri media region on the left side. There were no signs of intracranial haemorrhage or other recent pathology. Arterial and venous CT angiography showed no evidence of acute cerebral thrombosis or other vascular abnormalities. Electrocardiogram showed a normal sinus rhythm. Chest X-ray showed atelectasis of the right upper lobe. Laboratory results including a full blood examination, a metabolic panel and arterial blood gas analysis were within normal limits. Creatinine was 52  $\mu\text{mol/l}$  on admission with an estimated glomerular filtration rate (eGFR) above 90 ml/min/1.73 m<sup>2</sup> (CKD-epi).

Levetiracetam and baclofen are absorbed rapidly with a C<sub>max</sub> of 1.3 and 0.5-1.5 hours respectively.<sup>3</sup> Because of the late presentation with ingestion occurring at least nine hours earlier gastrointestinal decontamination was withheld. As co-ingestion of other substances was possible a routine urinary toxicology screening was performed which came back negative for all the included toxins (amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, methadone and opioids). The toxicological screening in blood revealed a paracetamol level of 10 mg/ml approximately nine hours after ingestion. This is in the non-toxic range and therefore the administration of N-acetylcysteine was discontinued.<sup>7</sup> The levetiracetam level was 26  $\mu\text{g/ml}$  (normal therapeutic range 5-25  $\mu\text{g/ml}$ ). No other drugs were found and ethanol was below the cut-off value.

The patient's consciousness gradually improved. Her vital signs remained within normal limits, as did her urine output. Subsequent metabolic panels showed no signs of acute kidney injury. Approximately 32 hours after ingestion she was awake and could be extubated. She told the treating physicians and her husband she only ingested levetiracetam and expressed her attempt as an act of impulse, which she regretted. Since levetiracetam is known to be associated with depressive mood disorders,<sup>5</sup> it was withdrawn and the patient was started on

lamotrigine. The next day the patient was discharged from our unit. The levetiracetam concentration was measured again 36 hours after ingestion and showed a level of 16  $\mu\text{g/ml}$  (figure 1). The elimination half-life (t<sub>1/2</sub>) was calculated based on the two concentrations and appeared to be 39 hours, which is 5-6 fold higher compared with t<sub>1/2</sub> value reported in healthy volunteers.<sup>4</sup>

**Figure 1.** Levetiracetam blood levels after ingestion of an overdose, with a t<sub>1/2</sub> of 39 hours



## Discussion

This case illustrates that despite the broad therapeutic window and mild adverse effect profile, levetiracetam overdose can be complicated by life-threatening symptoms. A recent case report and literature review on this subject reported three adult cases of an overdose with one patient requiring intubation and mechanical ventilation.<sup>8</sup> Exact doses corrected for weight were not always reported but the impression is that a high dose is not necessarily associated with severe symptoms (table 1).

So far levetiracetam blood levels were only reported for two cases and in comparison the level in our patient was low (table 1). However, even after careful re-evaluation of this case, we were not able to provide another explanation for her symptoms. Co-ingestion of other neuro-depressing drugs could be a reason for the marked decrease in consciousness in combination with a low levetiracetam level. The patient, however, repeatedly stated she ingested only levetiracetam and was not known to have access to drugs other than the ones mentioned above. Beside this, the urinary drug screen was negative. Although the patient's information could be incomplete or inaccurate and urinary drug screening is not specific and can be false-negative,<sup>11</sup> co-ingestion was considered unlikely.

With regards to the observed increase in half-life this cannot be attributed to renal dysfunction since the eGFR was normal at admission and the patient did not develop acute kidney injury. Despite the fact that doses up to 5 g of levetiracetam have shown first-order kinetics,<sup>4</sup> toxicokinetics can differ from pharmacokinetics and slow absorption of levetiracetam at high doses may have rate-limited the apparent half-life, as has been shown for other drugs.<sup>12-14</sup> The ingested dose of levetiracetam

**Table 1.** Previously reported cases of levetiracetam overdose

Reference	Age	Sex	Relevant medical history	Ingested dose	Levetiracetam blood levels	Symptoms	Intervention
Larkin et al. <sup>8</sup>	49 y	M	Seizures	358 mg/kg	Not available	Asymptomatic	Nasogastric lavage 6.5 hours after ingestion
Chayasirisobhon et al. <sup>9</sup>	41 y	M	Epilepsy	63 g	220 µg/ml 10 hours after ingestion	Blurred vision and mild ataxia	Activated charcoal 100 minutes after ingestion
Barrueto et al. <sup>10</sup>	38 y	F	Bipolar disorder	30 g	400 µg/ml and 72 µg/ml, 6 and 18 hours after ingestion	Vomiting 4 hours after ingestion, coma, respiratory depression	Orogastric lavage and activated charcoal 6 hours after ingestion, intubation

might not have distributed throughout the blood of the patient at the time the first serum sample was drawn because of a delay in absorption. The case Barrueto et al. reported, however, showed essentially the same half-life for an overdose of 30,000 mg when compared with a dose of 5000 mg in healthy volunteers.<sup>10</sup> In contrast to this case, we chose not to perform gastrointestinal decontamination and this may have implicated ongoing absorption, which could potentially explain the observed differences in half-life.

Another potential explanation for the observed increase in half-life is accumulation of levetiracetam in adipose tissue, since the patient is obese. In pharmacokinetic animal studies, however, levetiracetam shows a rapid tissue distribution with concentrations approximating those in blood with the exception of lower concentrations in the lens and adipose tissue and higher concentrations in the kidney.<sup>4</sup> It remains unclear which doses were administered in these experiments and although these animal data suggest that accumulation in adipose tissue after administration of supratherapeutic doses is unlikely, it cannot be excluded in this case.

This case suggests that the serum level of levetiracetam is not necessarily related to the presenting symptoms, as was previously shown for tricyclic antidepressants.<sup>15</sup> Animal studies showed a delay in the peak level of levetiracetam in brain consistent with a longer half-life in the central nervous system.<sup>16</sup> This might explain why a patient is still comatose even if the plasma levels are in the range of the upper limit of normal. The presence of preexisting cerebral damage may have contributed to the symptoms as this may have decreased tolerance for neuro-depressing drugs.<sup>17</sup>

As in the other reported cases supportive measures were taken. Theoretically, haemodialysis can be used to eliminate levetiracetam since it is a small molecule (170 Daltons), which

is highly soluble in water and has a low volume of distribution (0.5-0.7 l/kg) and protein binding.<sup>4</sup> In an experimental setting plasma levetiracetam concentration was decreased by 50% after four hours of haemodialysis in five ESRD patients.<sup>18</sup> To our knowledge haemodialysis has not been reported in cases of levetiracetam overdose. It may be a valuable treatment option in patients with coma and a decreased renal function causing a prolonged half-life.

Premarketing studies showed an increase in the incidence of behavioural abnormalities resulting in cessation of the treatment with levetiracetam in 0.4-3.9%.<sup>19</sup> Mula et al. reported an incidence of psychiatric adverse events in 10.1% with an incidence of 0.7% for suicidal ideation in 517 patients without a correlation between the dose of levetiracetam and the rate of events.<sup>20</sup> Following this and other reports of higher rates of patients experiencing psychiatric effects the manufacturers issued a warning for the use of levetiracetam in patients who may be predisposed to psychiatric disorders.<sup>19</sup> In hindsight our patient might have suffered from this side effect.

### Conclusion

Although levetiracetam is generally thought to be safe because of its broad therapeutic window and mild adverse effect profile, this case shows that serious side effects may occur. Attempted suicide has been reported as a side effect and withdrawal of levetiracetam should be considered in patients expressing symptoms of depression. Our findings in combination with earlier reports suggest that symptoms of overdose may be independent of the ingested dose and that serum levels do not always correlate with the severity of symptoms. Finally this case shows that analysis of levetiracetam levels in an intoxicated patient can only be used as an adjunct in diagnosis and forms no substitute for careful history taking and clinical assessment.

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