Case Report

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Levetiracetam and topiramate poisoning: Two overdoses on those drugs with no lasting effects

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Summary **Levetiracetam and topiramate are newer anticonvulsants, which is why international data on overdoses of these drugs are lacking. Only a few mild adverse reactions have been noted. These anticonvulsants have been the drug of choice for neurologists. Despite their wide usage, there is a dearth of literature on symptoms and signs of their toxicity. Presented here is the case of a 21-year-old female who overdosed twice on levetiracetam and topiramate. The woman was admitted and discharged after the first overdose. Ten days later, she took multiple tablets of both drugs and was seen again. Amazingly, the woman went home after the incident with no complications at all.**

Keywords: Anticonvulsants, toxicity, seizures, gastrointestinal decontamination, activated charcoal

1. Introduction

Levetiracetam entered the market in 2000 when it was approved by the US Food and Drug Administration (FDA) (*1*). Levetiracetam is currently being used for partial seizures and as an adjunctive therapy for generalized tonic-clonic convulsions (*1-3*). The mechanism of action of levetiracetam involves its effect on the intraneuronal concentration of calcium and amelioration of the inhibition of gamma-aminobutyric acid (GABA) and glycine channels. Additionally, levetiracetam has a favorable pharmacokinetic profile with quick absorption through oral intake, superb bioavailability, rapid attainment of steady-state concentrations, linear kinetics, and minimal plasma protein binding (*2*). Levetiracetam is not metabolized by the cytochrome P450 system but by the enzymatic degradation of its acetamide group (*1,2*). If it is administered orally, its absorption is not affected by food material. Less than 10% of levetiracetam binds to plasma proteins and levetiracetam has a bioavailability of 95%. Its half-life is 6-8 hours. The recommended adult dose is 1 g/day and can be increased to 3 g/day at 2 weeks (*2*).

Topiramate, a sulfamate-substituted monosaccharide, is a relatively new anticonvulsant agent. It is indicated as a monotherapy or adjunctive therapy to alleviate partial seizures, generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. Topiramate is also being used in the treatment of migraines, cluster headaches, essential tremors, binge eating disorders, acute mania, Tourette's syndrome, neuropathic pain, bipolar disorder, alcohol dependence, excess body weight, and smoking (*4,5*). Structurally, topiramate is unrelated to other anticonvulsants and acts by multiple neurostabilizing processes (*6,7*). The recommended adult dosage ranges from 200-400 mg/day. Topiramate peaks 2-3 hours after oral administration and its plasma elimination half-life is 18-24 hours (*6,8*). Its excretion is primarily (55-66%) *via* the kidneys (*7*).

2. Case Report

A young woman 21 years of age who was thin and lean (43.7 kg) and who had been an epileptic since the age of 5 was brought to the ER following ingestion of 40 tablets of levetiracetam 1 g and 60 tablets of topiramate 25 mg nearly 1.5 hours prior. This means she took 60 g of levetiracetam (20 times the maximum dose) and 1.5 g of topiramate (4 times the maximum dose). Her epilepsy was partially controlled and her last seizure

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occurred nearly a year prior. She was fully active and conscious in the ER. No drowsiness or difficulty breathing was observed. There were no complaints of any abdominal discomfort, nausea, or vomiting. Results of a general physical examination were normal. Gastrointestinal decontamination was done with 50 g of activated charcoal. The patient began vomiting and vomitus showed streaks of white material along with tiny fragments of tablets. A complete blood count (CBC), urea levels, creatinine levels, urinary calcium excretion (UCE), amylase levels, results of a liver function test (LFT), and an electrolyte and coagulation profile were all normal. An electrocardiogram (EKG) showed normal sinus rhythm. An examination of levetiracetam and topiramate levels in the blood was not possible at this facility. The woman was admitted to the general ward and closely monitored and observed. The next day, she was behaving normally and there were no complaints. She ate a full meal and her status was completely normal, so was discharged after 24 hours.

Ten days later the woman was seen again after she took multiple tablets of the same drugs 1 hour prior. At the time, she had taken 30 tablets of levetiracetam 1 g and 7 tablets of topiramate 25 mg. As in the previous incident, she was hemodynamically stable, fully active, and conscious. She had no gastrointestinal complaints. No drowsiness or lethargy was observed. She started vomiting after ingesting activated charcoal. Small pieces of tablets and white streaks were found in vomitus. Levels of the 2 drugs in blood could not be measured, but baseline values for the CBC, UCE, LFT, amylase, the electrolyte and coagulation profile, and arterial blood gases revealed no abnormalities. The patient was kept under close observation in the general ward. The next day, she was completely normal, eating, chatting, and roaming around normally. She was discharged 24 hours after admission in healthy condition.

3. Discussion

Topiramate is a newer anti-epileptic and is used as a monotherapy or in combination with other agents (*8*). It is also indicated in the treatment of psychiatric illnesses. Several cases of an accidental overdose in children or an intentional or suicidal overdose in older individuals have been reported (*6,9*). At therapeutic levels, topiramate is benign, and the most prevalent adverse reactions are dizziness, somnolence, and ataxia. However, acute psychosis, hepatic failure accompanied by encephalopathy, hyperthermia, hyperchloremic metabolic acidosis, nephrolithiasis, and parasthesia have also been reported (*5,8,10,11*). Beer *et al*. reported a death following an overdose of topiramate and other drugs (*6*). A retrospective study of anticonvulsant overdoses by Wills *et al*. indicated that 43% of patients had no symptoms and 34% had mild symptoms, while only 2o patients (4%) were severely affected (*10*). The patient reported by Lynch *et al*. was brought in unresponsive after intoxication (*8*). However, the current patient was brought in fully conscious and remained conscious on both occasions. Ozer and Altunkaya noted high anion gap metabolic acidosis 7 days after a topiramate overdose (*11*). Three of the 6 patients reported by Wisniewski *et a*l. had metabolic acidosis after a topiramate overdose (*5*). In the current case, however, a metabolic imbalance was not noted when the patient was brought in the second time. Christian *et al*. and Anand *et al*. reported seizures after a topiramate overdose (*4,9*), but the current patient remained absolutely normal.

Levetiracetam has recently been approved and is used as adjunctive therapy for the treatment of adult patients with partial seizures with or without secondary generalization that are refractory to other antiepileptic drugs (*12*). A multicenter, double-blind, and randomized trial clearly indicated that levetiracetam significantly reduces the frequency of partial seizures. A study by Harden *et al*. found it well-tolerated and without risks (*13*). According to Wills *et al*., patients only had some gastrointestinal (GI) problems and levetiracetam appeared to have the lowest toxicity (*10*). This may be due to the fact that levetiracetam is mostly excreted as-is in urine, although 24% is hydrolyzed to an inactive metabolite in the blood (*2*). The patients reported by Vellinga *et al*. and Barrueto *et al*. experienced respiratory distress after intoxication and needed endotracheal intubation, though they did recover in 24 hours (*2,14*). In contrast, the current patient overdosed twice within a short period of time but her condition remained completely normal throughout observation and she was discharged safely and in healthy condition.

4. Conclusion

To the extent known, there are no reported cases of overdoses involving both topiramate and levetiracetam. The striking feature of the current case is that the patient heavily overdosed twice with these two antiepileptic agents in a short span of time. Amazingly, the patient had no lasting effects and her condition returned to normal after both incidents. She experienced no psychological or biochemical complications, but a few cases of respiratory distress that ultimately required definitive airway protection have been reported. The bottom line is that strict vigilance is mandatory several hours after overdoses involving both topiramate and levetiracetam.

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