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Hofer, K E ; Trachsel, C ; Rauber-Lüthy, C ; Kupferschmidt, H ; Kullak-Ublick, G A ; Ceschi, A

DOI: https://doi.org/10.1016/j.yebeh.2011.02.023

Moderate Toxic Effects following Acute Zonisamide Overdose

Katharina E. Hofer,[1] Christian Trachsel,[2] Christine Rauber-Lüthy,[1] Hugo Kupferschmidt,[1] Gerd A. Kullak-Ublick,[3] and Alessandro Ceschi[1]

[1]Swiss Toxicological Information Centre, Zurich, Switzerland
[2]Medical Clinic and Intensive Care, Hospital of Uster, Uster, Switzerland
[3]Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland

Corresponding author:

Alessandro Ceschi, MD
Head, Division of Science
Swiss Toxicological Information Centre
Freiestrasse 16
CH-8032 Zurich
Tel: +41-44-634-1034
Fax: +41-44-252-8833
e-mail: Alessandro.Ceschi@usz.ch

Abstract

Zonisamide is an antiepileptic drug that acts on voltage-sensitive sodium and calcium channels, with modulatory effect on GABA-mediated neuronal inhibition and inhibitory effect on carbonic anhydrase. It is mainly used for the treatment of partial seizures, and is generally well tolerated at therapeutic doses. The most common reported adverse effects are somnolence, anorexia, dizziness, and headache. Zonisamide overdose data are limited in the literature and no case of zonisamide monointoxication has been published to date. We report the first case of zonisamide monointoxication in a 25-year-old female who ingested 12.6 g of this substance with suicidal intent. Despite a plasma zonisamide concentration of 182 mg/L at admission, the patient showed a benign clinical course with vomiting and CNS depression, requiring brief intubation. Somnolence persisted for 50 hours, normal-anion-gap metabolic acidosis and polyuria for several days. Complete recovery may be expected with supportive care, even after ingestion of large zonisamide overdoses.

Keywords

Zonisamide; antiepileptic drugs; toxicity; poisoning; suicide attempt; clinical course; metabolic acidosis.

1. Introduction

Zonisamide (ZNS), a sulfonamide derivative, is an anti-epileptic drug (AED) that acts on voltage-sensitive sodium and T-type calcium channels [1,2], blocking potassium-evoked glutamate response [3]. ZNS modulates GABA-mediated neuronal inhibition [4] and weakly inhibits carbonic anhydrase (CA) activity [5]. ZNS also affects dopaminergic and serotonergic neurotransmission [6]. For more than two decades, ZNS has been used as monotherapy and adjunctive therapy for the treatment of partial and generalized seizures in pediatric and adult patients in Japan [7]. ZNS was approved in the United States in 2000, and in Europe in 2005, for adjunctive treatment of partial seizures in adults. Additional evidence exists for ZNS as an effective monotherapy – off-label use – against complex partial seizures, generalized seizures and partial seizures secondarily generalized [8]. ZNS is also used off-label for other disorders such as chronic pain, Parkinson's disease, restless legs syndrome, and migraine [8,9,10]. ZNS is generally safe and well tolerated at therapeutic doses. The most commonly reported adverse effects associated with ZNS use were somnolence, anorexia, dizziness, headache, nausea, and agitation–irritation in a retrospective case study [11]. Although epileptic patients have a high incidence of psychiatric comorbidities with depression being the most common diagnosis [12], and AEDs are common agents taken in intentional drug overdose [13], limited data exist on overdose of ZNS, and to our knowledge no case of ZNS monointoxication has been published to date. There are two cases of ZNS poisoning reported in the literature, but in both, other AEDs in overdose were coingested [14,15].

2. Case report

A 25-year-old Caucasian woman with a history of simple and complex focal seizures, and secondarily generalized seizures since the age of 20 years, which were treated with 300 mg ZNS, 5 mg clobazam, and 150 mg lacosamide daily, was brought to the emergency department 8 hours after ingestion of 12.6 g of ZNS (126 x 100 mg-tablets) with suicidal intent. The patient was also known to have a diagnosis of emotionally unstable personality disorder and depression, with earlier suicide attempts documented in her medical records. Her husband, who was permanently next to the patient before arrival at the hospital, observed vomiting and increasing somnolence, but no other symptoms. At admission, the patient was obtunded

(Glasgow Coma Scale score 9) and vomited repeatedly. Pulse rate was 87 beats/ min, blood pressure 103/54 mmHg, respiratory rate 20 breaths/min, and the body temperature was 35.8 °C. ECG showed mild QRS widening (102 ms) and QT prolongation (QTc 506 ms). Complete blood count revealed an elevation of white blood cells (17 x 10^9/L); all other values were within normal limits. The patient was intubated for airway protection, and a single dose of activated charcoal was administered by gastric tube. Arterial blood gas analysis (ABGA) after intubation showed a moderate lactic acidosis (pH 7.28, pCO2 5.19 kPa, pO2 20.1 kPa, bicarbonate 28.4 mmol/L, BE -7.3 mmol/L, lactate 5.5 mmol/L). Hemodialysis for enhanced elimination of ZNS [16] was not performed, because the patient's vital signs remained stable. The patient's level of consciousness improved within 8 hours from admission, and she was therefore extubated. She remained somnolent for another 50 hours, and transient generalized myoclonus and diplopia occurred. The following day (28 hours after admission), the ECG showed a normal QRS complex (90 ms) and the corrected QT interval decreased to 458 ms. The ECG was normal three days after admission (QRS 85 ms, QTc 398 ms). ABGA showed a normal-anion-gap metabolic acidosis with partial respiratory compensation (pH 7.34, pCO2 3.7 kPa, pO2 13.0 kPa, bicarbonate 17.0 mmol/L, BE -9.7 mmol/L, lactate 0.5 mmol/L, chloride 117 mmol/L, sodium 136 mmol/L). This alteration gradually improved over the next 3 days, and there was no need for intravenous bicarbonate administration. Polyuria without alteration of other renal parameters was persistent at discharge (day 7).

Laboratory analysis on admission (8 hours after ingestion of the AED) revealed a plasma ZNS concentration of 182 mg/L (therapeutic 10-40 mg/L [10]; high-performance liquid chromatography). The markedly increased plasma ZNS concentration was confirmed in a second blood sample collected at the same time: 202 mg/L. Moreover, therapeutic levels of clobazam (1.9 µmol/L; liquid chromatography-mass spectrometry) and lacosamide (4.4 µmol/L; high-performance liquid chromatography) were measured. A serum toxicological screening was positive for midazolam and ephedrin (both administered during intubation) and caffeine; no other substances were detected. Urine drug screening was positive for benzodiazepines, and negative for drugs of abuse. Plasma ZNS concentration repeated at discharge (day 7) was 1.8 mg/L. Therapeutic drug monitoring of ZNS one month before admission revealed a plasma concentration of 26.5 mg/L.

3. Discussion

From previous studies it is known that ZNS is rapidly and completely absorbed after oral administration with peak plasma concentration achieved within 2-5 hours [17]. Following a 300 mg ZNS oral dose, a peak concentration of 3.48 mg/L can be expected [18]. In accordance with these data, plasma ZNS concentrations around 180-200 mg/L were measured in our patient 8 hours after ingestion of 12.6 g ZNS. It has been shown that ZNS displays a linear pharmacokinetic in the therapeutic dose range [19]. There is some evidence that this may apply also to overdose conditions [14]. The plasma ZNS concentrations measured in our case on day 1 and day 7 are compatible with this elimination pattern.

In the medical literature there are only two reported cases of ZNS overdose, but in both, also other AEDs were coingested in overdose, so that it is difficult to ascribe the reported symptoms and signs to a specific drug. For example, in one of these reports, a 26-year-old female developed coma, spontaneous horizontal nystagmus, myoclonus, bradycardia, hypotension and respiratory depression after ingesting an overdose (precise dose unknown) of ZNS and clonazepam. The high plasma concentrations of both ZNS (100.1 mg/L) and clonazepam (376 µg/L; therapeutic range 15-60 µg/L) measured 31 hours after the suicide attempt, suggest that the patient's comatose state was probably due to a combined effect of both AEDs which were ingested in overdose. In this case, the estimated maximal plasma ZNS concentration by extrapolation was 143 mg/L [14].

In the other article, the clinical course of a 27-year-old woman who committed suicide with a mixed overdose of lacosamide (12 g), gabapentin (56 g), topiramate (2 g) and ZNS (2.8 g) is described. The patient was found comatose, and experienced repeated generalized seizures. Hypotension and an increase in the PR interval were documented. Blood concentrations of topiramate and ZNS were not measured until the day after admission, and were within normal limits (ZNS 18 mg/L, topiramate 3.7 mg/L). Although lacosamide plasma concentration was not measured, most symptoms and signs were attributed to this drug [15].

Our patient showed symptoms and signs that are consistent with the adverse effects of ZNS observed in clinical trials, and which involved mainly the central nervous system, such as somnolence, anorexia, dizziness, ataxia, agitation/irritability and

vomiting as the most frequent, and more rarely nystagmus, diplopia and myoclonus. Beside CNS effects, our patient showed a normal-anion-gap acidosis and polyuria, which persisted significantly longer than the neurological effects. The metabolic acidosis presumably results from the inhibition of renal cortical CA, which is also reported in overdose with topiramate [20]. The inhibition of CA seems to play a minor role in the drug's anticonvulsant activity, however ZNS seems to have an even more selective inhibitory effect than topiramate on CA isoform II and IV, both strongly expressed in the kidney [5]. However, the metabolic acidosis resulting from the ZNS-mediated inhibition of renal cortical CA, seems to be of minimal clinical significance.

Seizures were not observed during the 7-day hospitalisation period, although exacerbation of seizure activity has been described in association with overdose of several AEDs, also with the newer drugs [21]. Presumably the patient had sufficient seizure protection by her medication with clobazam and lacosamide.

QRS widening and QT prolongation have not been previously described in ZNS overdose and deserve further confirmation, although widening of the QRS complex has been reported in poisoning with drugs that block voltage-sensitive sodium channels. For example, in a case of lamotrigine overdose, a QRS of 112 ms has been documented [22].

In conclusion, ZNS appears to be relatively safe in overdose. Due to the long serum half-life (50-70 h) of this drug [23], symptoms can persist for several days, but complete recovery can be expected with supportive care.

Informed consent

Written informed consent was obtained from the patient for publication of this case report.

Conflict of interest statement

The authors have no conflict of interests to declare.

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