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Selected Topics: Toxicology

LACOSAMIDE OVERDOSE: A CASE OF QRS PROLONGATION AND SEIZURE

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☐ **Abstract—Background: Lacosamide is a third-generation antiepileptic drug. Its likely mechanism of action is via neuronal sodium channel blockade, via a unique manner compared with other antiepileptic drugs that block sodium channels. A paucity of information exists regarding lacosamide overdosage. Lacosamide overdosage is thought to cause QRS prolongation and seizures, due to its effect of sodium channel blockade. The potential efficacy of sodium bicarbonate to reverse the effects of lacosamide has not been well studied. Furthermore, prior reports of lacosamide toxicity have occurred in the setting of concomitant polypharmacy. Thus, the isolated toxic effects of the drug have not been well elucidated. Case Report: We report a case of a suspected, single-ingestion overdose on lacosamide. The patient developed signs of cardiotoxicity and seizure. Why Should an Emergency Physician Be Aware of This?: After lacosamide overdosage, the emergency physician must be capable of acute management of subsequent lacosamide toxicity. Understanding the mechanisms of action causing toxicity due to this drug can help the clinician to anticipate the interventions that may be needed or useful to treat this potentially toxic ingestion. Published by Elsevier Inc.**

☐ **Keywords—lacosamide; sodium channel blockade; seizure; bicarbonate**

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INTRODUCTION

Lacosamide is a third-generation antiepileptic drug that is used as monotherapy or adjunctive therapy for epilepsy (1). Its proprietary name is "Vimpat." The mechanism of action of lacosamide is believed to occur via neuronal sodium channel blockade, in a unique manner compared with other antiepileptic drugs that affect the activity of sodium channels (2).

Limited data exist regarding the toxicologic characteristics directly due to lacosamide alone in an acute overdose state. Most prior reports of lacosamide toxicology have been derived from polypharmacy ingestions, in which lacosamide was but one of several drugs exerting toxicologic effects. The presence of such polypharmacy is likely to have confounded a full understanding of the toxic effects due to lacosamide alone (1,3,4). Cardiotoxicity, manifesting as widening of QRS complexes on the electrocardiogram, and central nervous system toxicity, manifesting as seizures, have been reported (3–7).

There is a paucity of information, not only regarding isolated lacosamide overdosage, but also regarding any potential efficacy of sodium bicarbonate to treat cardiotoxic effects from the drug.

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We report a case of suspected isolated lacosamide overdosage that presented with central nervous system and cardiovascular system toxicity, and was treated with sodium bicarbonate.

CASE REPORT

A 48-year-old woman weighing 96 kg presented to the Emergency Department (ED) after an acute lacosamide overdose. She had been admitted the previous day to a mental health facility, due to suicidal ideation, and discharged from that facility on the following day (the day of presentation to our hospital). After discharge, she began throwing her belongings into the street outside the mental health facility. Police arrived on scene and witnessed the patient ingesting pills from a lacosamide bottle. The quantity of pills ingested was unknown, but her last prescription for 60 tablets of 100 mg was filled 5 months prior, and one tablet remained after the ingestion. She arrived to the ED by ambulance 15 min post ingestion, with emesis and visual hallucinations.

She had a past medical history of depression, traumatic brain injury, medication nonadherence, and convulsions that were poorly characterized and possibly related to her prior brain injury. Her other outpatient medications were levothyroxine, montelukast, ibuprofen, gabapentin, venlafaxine, doxepin, methadone, tramadol, hydroxyzine, and oxybutynin, in addition to lacosamide. The patient also endorsed a history of methamphetamine use.

Initial vital signs were: blood pressure 197/134 mm Hg, heart rate 100 beats/min, respiratory rate 20 breaths/min, temperature 36.3°C (oral), and SpO_2 100% on room air. On examination, she was agitated and oriented only to self. She reported ingesting lacosamide as a suicide attempt. Peripheral neurologic examination was without myoclonus or hyperreflexia. Pupils were 3 mm and reactive to light, and nystagmus was absent.

Serum electrolytes and renal function were within normal limits. Salicylate and acetaminophen concentrations were undetectable. Urine drug screen was positive for amphetamines and methadone. Electrocardiogram (ECG) showed QRS interval of 102 ms, which was prolonged from her baseline QRS interval of 88 ms, measured the prior day (Figure 1). At 2 h and 29 min post ingestion, the patient had a witnessed tonic-clonic seizure and was given lorazepam 1 mg i.v. An ECG at that time demonstrated a widening QRS interval of 106 ms. Therefore, sodium bicarbonate 50 mEq was administered. Minutes later, naloxone 0.4 mg i.v. was trialed for her depressed mental status, and the patient experienced a second seizure. At this point, she was intubated for airway protection. Repeat ECG obtained 17 min after bicarbonate demonstrated the QRS interval had continued to widen to 118 ms (Figures 1 and 2). Additional bicarbonate was not administered, and at 5.5 h post ingestion, the QRS interval had narrowed to 94 ms.

Continuous electroencephalography recording, initiated after intubation, accompanied by sedation with

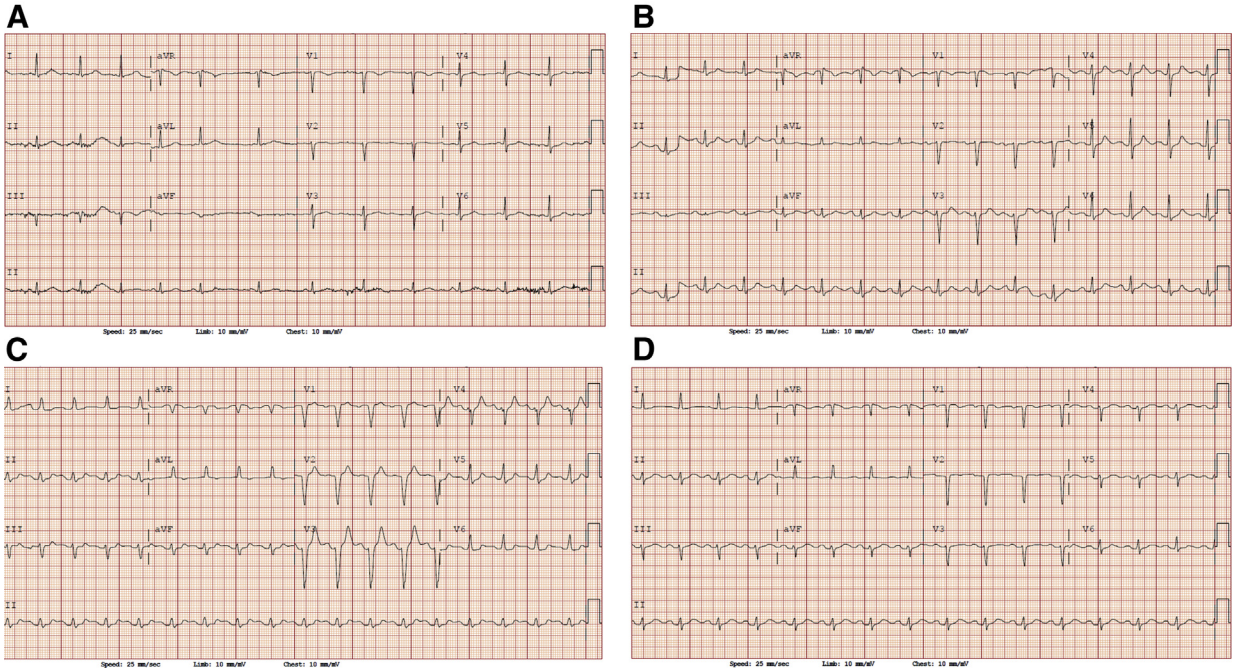

Figure 1. (A; top left) Baseline electrocardiogram (ECG) with QRS of 88 ms, obtained from visit 24 h prior to presentation. (B; top right) ECG with QRS of 102 ms, obtained 45 min post ingestion. (C; bottom left) ECG with QRS of 118 ms, obtained 2 h and 53 min post ingestion. (D; bottom right) ECG with QRS of 94 ms, obtained 5 h and 30 min post ingestion.

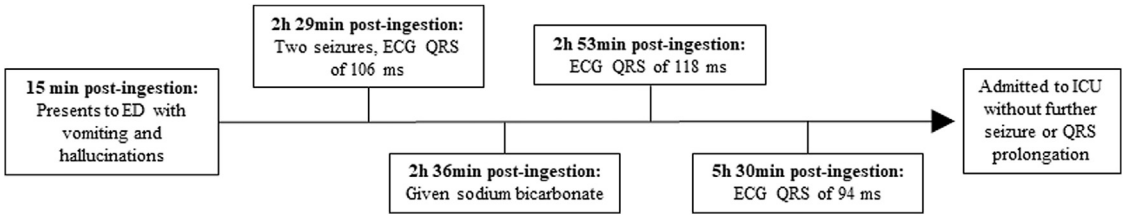

Figure 2. Timeline of initial evaluation and management of patient after lacosamide overdose. ED = emergency department; ECG = electrocardiogram; ICU = intensive care unit.

propofol, did not show any epileptiform activity. The patient remained hemodynamically stable and was treated supportively over the next 12 h in the intensive care unit. She was extubated the following day and transferred to the psychiatry service.

Serum lacosamide concentrations were assayed using a 5 × dilution and high-performance liquid chromatography-tandem mass spectrometry. Serum lacosamide from a sample drawn 4 h and 21 min after ingestion was 98.4 mg/L (therapeutic range 5–10 mg/L). By 11 h and 14 min post ingestion, the serum lacosamide concentration had decreased to 77.7 mg/L.

DISCUSSION

Lacosamide's proposed mechanism of action is via enhancement of voltage-gated sodium channel slow inactivation, a unique means of reducing neuronal hyperexcitability when compared with the mechanism of other sodium channel binding antiepileptic drugs, which modulate the fast inactivation of the sodium channel (2). Clinical use of lacosamide may increase in the future, given the suggested benefit from this drug for refractory epilepsy and status epilepticus, and disease modification secondary to modified neurite outgrowth (8,9).

Although the possibility of unacknowledged co-ingestions is always present, this case most likely represented an isolated lacosamide overdose, based on witness description, self-report after extubation, the observed serum lacosamide concentrations, a lack of physical examination findings suggestive of other toxidromes or ingestion, and a review of her home medication list. Most previously reported cases with measured serum lacosamide concentrations have been confounded by co-ingestions of lamotrigine, gabapentin, topiramate, zonisamide, cyclobenzaprine, and levetiracetam (3,4,10).

Cardiac arrest after lacosamide ingestion has been reported, but the etiology for that cardiac arrest is not fully clear from a single case report of cardiac arrest after an apparently isolated lacosamide overdose that was found to have caused only a mildly elevated serum lacosamide concentration (5). To our knowledge, this is the first report of a large-quantity isolated lacosamide overdose.

The patient in this case developed QRS prolongation. Given the dynamic nature of the QRS interval and lacosamide's expected effects upon sodium channel function in a single pharmaceutical overdose, this QRS change was likely attributable to lacosamide toxicity. In addition to QRS prolongation, lacosamide has been associated with PR prolongation, varying degrees of atrioventricular block, and sinus pauses (11,12). Three cases of cardiac arrest associated with lacosamide have been reported, one of which was reported in an abstract without further details (3,5,7). The QRS prolongation in this case is consistent with prior reports. In vitro work has confirmed the effect of lacosamide on cardiac sodium channels, and found that cardiac sodium channels are less susceptible to lacosamide blockade than neuronal sodium channels. Lacosamide's binding site on the sodium channel overlaps with binding sites for local anesthetics and batrachotoxin (13).

Three prior cases have administered sodium bicarbonate for lacosamide QRS prolongation; two described narrowing of QRS, and one found no significant change in QRS 8 h after bicarbonate (3,5,6). The efficacy of sodium bicarbonate for the management of lacosamide QRS prolongation was unclear in this case. Narrowing of the QRS can typically be expected within minutes of the administration of bicarbonate. However, in this case, 17 min after infusion of 50 mEq of sodium bicarbonate, the QRS actually further widened from 106 to 118 ms. Sodium bicarbonate's apparent lack of efficacy in this case may have been secondary to underdosing of sodium bicarbonate. It is also possible that the 50 mEq administered blunted even further widening of the QRS that may have occurred had bicarbonate not been administered, or that continuing gastrointestinal absorption of ingested lacosamide contributed to the further widening of the QRS complex.

This patient sustained two seizures. Seizure associated with lacosamide toxicity has been previously reported,

but one case involved co-ingestion of the pro-convulsant antiepileptic drug lamotrigine, and one case did not measure the serum lacosamide concentration (4,6). A poison center study found seizure to have occurred in 17% of lacosamide toxic cases (14).

Details of the possible prior seizure disorder in the patient who survived this ingestion were not well characterized by her past medical history, and although it cannot be determined with certainty whether her two seizures were primarily from lacosamide toxicity or an underlying seizure disorder, we believe they were most likely due to lacosamide toxicity. This is based on the timeline of apparent seizure after the witnessed acute ingestion, the observed dynamic QRS prolongation, and previous suggestions of seizure due to lacosamide ingestion that can be obtained from other reports.

This patient had significantly elevated lacosamide serum concentrations, which were many-fold above the recommended therapeutic range. Using the initial concentration, her weight, and the therapeutic volume of distribution of 0.6 L/kg, it is estimated the patient absorbed at least 5667 mg, or approximately 57 tablets of lacosamide. Based on the two measured concentrations, estimate of the drug's elimination half-life using first-order kinetics was 31.9 h. This is significantly prolonged compared with the 13-h half-life at therapeutic dosing, and the 15–20-h half-life with a peak serum concentration of 53.9 mg/L reported by Deslandes et al. (4,15). Although Deslandes et al. did not detail how they estimated the drug's half-life, their graph visually resembles first-order elimination, and at therapeutic dosing, lacosamide is known to have first-order elimination (4). Lacosamide's elimination at therapeutic dosing relies on approximately 40% unchanged renal elimination, < 30% hepatic biotransformation to the O-desmethyl metabolite, 20% polar serine derivatives, and < 2% other metabolites (15). This patient had normal renal function and no known prior history of hepatic disease. Lacosamide is considered to have low potential for P450 interactions, and we do not expect her home medications to have significantly affected its metabolism. Lacosamide is not significantly ionizable at physiologic pH, and therefore, urine pH is unlikely to affect the elimination half-life. The apparently prolonged elimination half-life in this case, compared with that of Deslandes et al., may reflect ongoing absorption of the drug from the gastrointestinal system, as no gastric decontamination was undertaken (4). Alternatively, the prolonged half-life may suggest a previously unreported event, a saturation of a metabolic pathway leading to destruction of the drug molecule, with possible accompaniment by "Michaelis-Menten" pharmacokinetics.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

In summary, clinical use of lacosamide as a third-generation antiepileptic drug may increase in the future. In overdoses, the emergency physician is likely to encounter the acute management of toxicity from lacosamide. Understanding the toxicity will help the clinician to anticipate what interventions will be needed to treat patients with this potentially toxic ingestion.

This case report describes a suspected isolated and large lacosamide ingestion, which resulted in seizures and QRS prolongation on the electrocardiogram. It is unclear whether the administration of bicarbonate had efficacy as a potential antidote. Prolongation of the elimination half-life was also demonstrated, compared with a prior case report that reported a markedly shorter half-life after overdose in association with a concentration that was many-fold lower than was observed in this case. This prolongation may suggest a saturation of a metabolic pathway that may follow Michaelis-Menten kinetics.

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