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Evolving Electrocardiographic Changes in Lamotrigine Overdose: A Case Report and Literature Review

Patricia Chavez · Abel Casso Dominguez · Eyal Herzog

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Abstract Lamotrigine overdose usually follows a benign pattern, and the majority of cases reported involve a co-ingestant. Prior reports have suggested the possible use of intravenous lipid emulsion in cases of severe sodium channel blockade. We describe the electrocardiographic changes in a massive lamotrigine overdose treated with intravenous lipid emulsion. A 36-year-old male with bipolar disorder ingested 13.5 g of lamotrigine in a suicidal attempt. The lamotrigine level was 78.0 μg/mL. Comprehensive drug screen was negative for all screened compounds. The electrocardiogram demonstrated a prolonged QRS complex and signs suggestive of sodium channel blockade. Refractory to treatment with sodium bicarbonate was treated with intravenous lipid emulsion, with immediate resolution of the electrocardiographic changes. Lamotrigine inhibits the voltage-gated sodium channel opening, attenuating the release of excitatory neurotransmitters. Cardiac intraventricular conduction could be delayed in cases of lamotrigine overdose resulting in QRS and QTc prolongation and R waves >3 mm in leads I and aVR. A potential role for intravenous lipid emulsion therapy has been described in patients with toxic levels of lamotrigine and electrocardiographic changes refractory to the treatment with sodium bicarbonate. Intravenous lipid emulsion has been successfully used in the treatment of lamotrigine cardiac toxicity.

Keywords Lamotrigine · Intravenous lipid emulsion · Electrocardiogram · Intraventricular conduction delay

Introduction

Lamotrigine is a phenyltriazine compound approved for the treatment of generalized seizures, partial seizures, Lennox–Gastaut syndrome, and bipolar disorder [1]. This agent inhibits the voltage-gated sodium channel opening, thereby stabilizing the pre-synaptic membrane and attenuating the release of excitatory neurotransmitters under conditions of sustained repetitive neuronal firing, primarily glutamate [2]. Lamotrigine also inhibits serotonin, norepinephrine, and dopamine reuptake [3]. Serum lamotrigine levels greater than 14 μg/mL are potentially toxic [4]. Cases of overdose are rarely reported in the literature, and often, unlike the case presented below, there is history of a co-ingestant and the clinical course follows a benign pattern [5]. The most common adverse effects of lamotrigine are drowsiness, lethargy, rash, vomiting, nausea, and ataxia, but it can also be associated with major clinical events, including coma, seizures, and respiratory depression [6].

We present this case to describe the electrocardiographic changes in a massive lamotrigine overdose and emphasize the possible use of intravenous lipid emulsion (ILE) for the treatment of ventricular arrhythmias refractory to sodium bicarbonate.

P. Chavez · E. Herzog
Division of Cardiology, St. Luke's - Roosevelt Hospital Center, Mount Sinai Health System, Icahn School of Medicine, New York, NY 10025, USA

A. Casso Dominguez (✉)
Department of Medicine, St. Luke's - Roosevelt Hospital Center, Mount Sinai Health System, Icahn School of Medicine, 1111 Amsterdam Avenue, New York, NY 10025, USA
e-mail: acassodominguez@chpnet.org

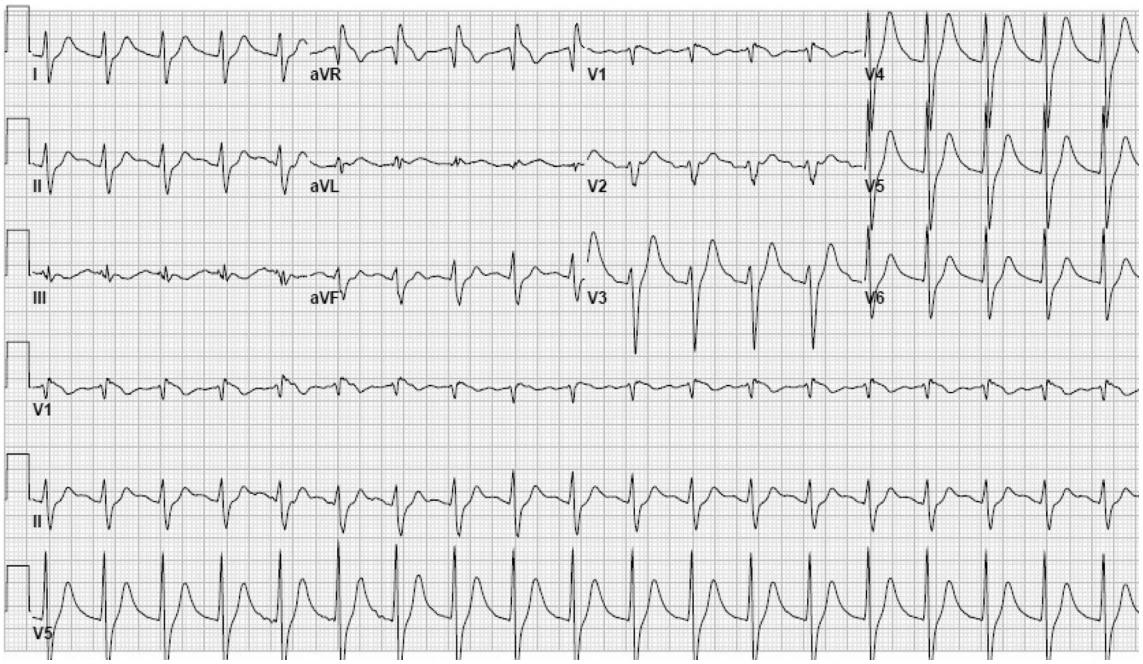

Fig. 1 Admission ECG. Sinus tachycardia at a rate of 110 beats per minute, a new right bundle branch block, QRS duration of 128 ms, QTc of 458 ms, and R waves >3 mm in leads I and aVR, suggestive of sodium channel blockade

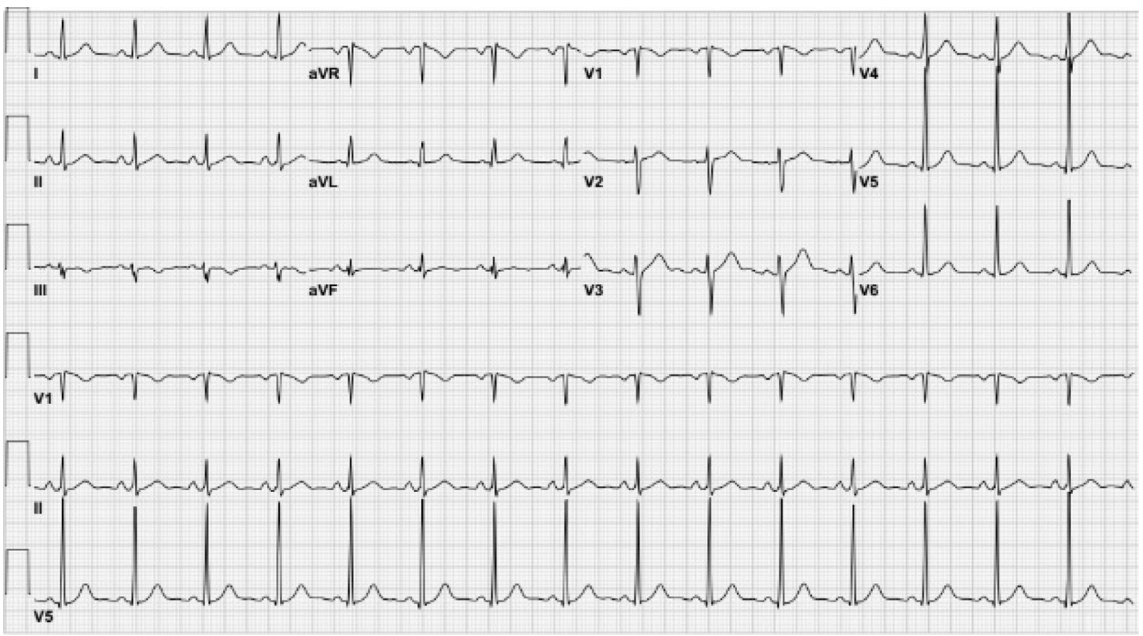

Fig. 2 Post-intravenous lipid emulsion therapy ECG, with normalization of QRS and QTc

Case Report

A 36-year-old male was brought into the emergency department (ED) after being found on the floor and experiencing witnessed involuntary movements that lasted approximately 5 min. On arrival to the ED, the patient's blood pressure was 150/80 mm Hg, the pulse 68 beats per minute, the respiratory rate 24 breath per minute, temperature 36 °C by oral measurement, and the oxygen saturation 95 % while breathing ambient air. The patient's capillary blood glucose level was 116 mg/dL.

On examination, he was noted to be oriented to person only, opened his eyes to voice, but was unable to follow any commands. The pupils were 3 mm in diameter and

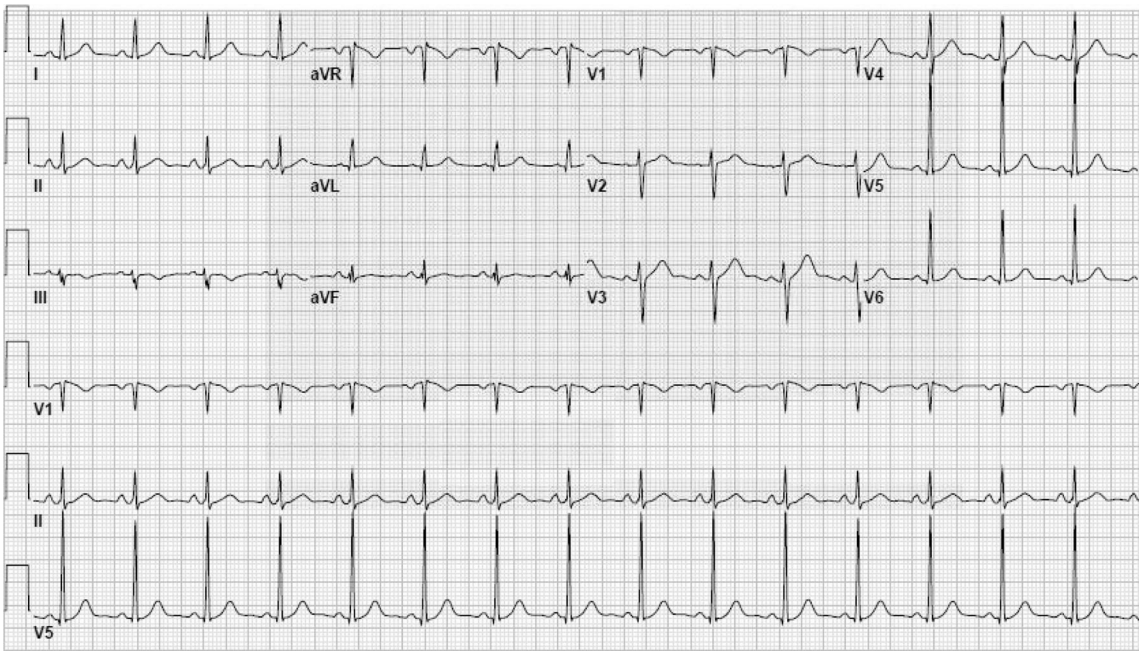

Fig. 3 ECG at discharge, normal sinus rhythm, without QRS/QTc abnormalities

minimally reactive to light. The neck was supple. The heart, lungs, and the remainder of the physical examination were unremarkable. The patient had spasticity with resistance to motion both with flexion and extension of all extremities. No evidence of tremor, myoclonus, or chorea was noticed. An examination of the cranial nerves appeared normal. Plantar flexor responses were bilateral.

The patient had been diagnosed with Human Immunodeficiency Virus (HIV) 5 years ago, with the most recent CD4+ count being >1,000 cells/mL. He also had a history of bipolar disorder, a prior suicidal attempt, and polysubstance abuse, including benzodiazepines, cocaine, and alcohol. His medication regimen consisted of raltegravir 400 mg twice daily, emtricitabine 200 mg daily, tenofovir 300 mg daily, and lamotrigine 150 mg immediate release twice daily. Upon further questioning, his partner revealed that the patient recently had stopped taking his medications.

Within 1 h after arrival to the ED, the patient had generalized tonic–clonic seizures that led to status epilepticus. He was intubated for airway protection after the administration of lorazepam and propofol. An electrocardiogram (ECG) done on arrival to the ED is shown in Fig. 1. A computed tomography (CT) of the brain without contrast did not show any acute intracranial hemorrhage or mass.

Results of the initial laboratory workup, obtained at the time of the first seizure, included a WBC of 13.7 K/μL, hemoglobin of 15.4 g/dL, and platelet count of 385 K/μL. A complete metabolic panel was normal with the following exceptions: The serum bicarbonate concentration was 13 mmol/L and the serum lactic acid level was 16 mmol/L. The venous blood gas while breathing ambient air demonstrated a pH of 7.15, pCO_2 46 mmHg, and pO_2 29 mmHg. Cerebrospinal fluid analysis was normal and was tested negative for HSV, EBV, CMV, VZV, Toxoplasma, M. pneumoniae, and Syphilis. Urine toxicology screening was negative for cocaine, amphetamines, opiates, and barbiturates. Tests for salicylates, acetaminophen, carbamazepines, phenytoin, lacosamide, and ethanol were negative.

The patient was admitted to the medical intensive care unit where he received activated charcoal and continuous veno-venous hemofiltration (CVVH) with bicarbonate solution 8.4 %. One hour later, a repeated ABG showed normalization of the pH, but the ECG revealed persistent prolongation of the QRS complex and the QTc. A single 150 mL (1.5 mL/kg) bolus of 20 % intravenous lipid emulsion was given. Following the ILE administration, an ECG showed immediate narrowing of the QRS and normalization of conduction abnormalities, as shown in Fig. 2. ILE was continued for the next 12 h at a rate of 0.5 mL/kg/min.

The missing pill count of his bottle of lamotrigine estimated the amount ingested as up to 13.5 g (90 tablets of 150 mg). The serum lamotrigine level 2 h after the presumed time of ingestion was 78.0 μg/mL (reference 3–14 μg/mL). Tests for carbamazepine, phenytoin, and lacosamide levels were all undetectable.

Eight hours after his presentation, an electroencephalogram (EEG) demonstrated persistent generalized seizures,

requiring phenobarbital for management. A magnetic resonance imaging (MRI) of the brain with contrast was normal, a transthoracic echocardiogram (TTE) was unremarkable, and no atrial septal defect was detected.

Over the next week, the patient was successfully weaned off from mechanical ventilation, and the CVVH therapy was stopped; however, his mental status never returned to baseline. He developed functional quadriplegia, with electromyography and muscle biopsy results suggestive of critical illness myopathy. An ECG prior to discharge is shown in Fig. 3. Lamotrigine was discontinued, and the patient was discharged to a rehabilitation facility on paliperidone as a mood stabilizer.

Discussion

Cardiac toxicity has been suggested to be mediated by sodium channel blockade in cases of lamotrigine overdose [7]. The alpha subunit in the voltage-gated type V sodium channel (SCN5a) is found predominantly in the cardiac myocytes, and mutation of the gene encoding for this protein has been associated with Brugada syndrome, Romano–Ward syndrome, sick sinus syndrome, and heart block, among others [8, 9]. The phase 0 of the cellular action potential is slowed by sodium channel blockade with variable serum lamotrigine levels, resulting in QRS and QTc prolongation and R wave >3 mm in leads I and aVR [10, 11].

The electrocardiographic changes are usually self-limited. In cases of persistent QRS complex prolongation and ventricular arrhythmias, the administration of sodium bicarbonate has been reported to induce QRS complex narrowing, as it decreases the ionized portion of the drug and attenuates its toxicity [12].

The role of hemodialysis (HD) in acute intoxication for lamotrigine is not completely understood. At therapeutic dosing, a 20 % extraction rate with hemodialysis has been reported, but significant individual variation was acknowledged [13]. A recent report showed the successful removal of lamotrigine in overdose with the use of hemodialysis; however, further studies using HD clearance rates and dialysate concentrations are needed for a more definitive conclusion [12].

A potential role for ILE has been described in patients with toxic levels of lamotrigine [14]. The exact mechanism of action of ILE remains only partially understood, but three possible mechanisms have been proposed. The first suggests a formation of an expanded lipid compartment within the intravascular space that decreases the free drug levels and thereby toxicity; the second proposes that ILE increases the cardiac myocytes calcium levels, increasing their inotropic action; and the third one talks about the enhancement of the fatty acid transportation in the inner mitochondrial membrane [15].

In a recent case series of lamotrigine overdose, one of the cases reported the use of ILE after 60 h of refractory agitation, but no details were reported of the electrocardiographic changes and/or the clinical outcome of this patient [5]. A multicenter retrospective chart review of patients receiving ILE for drug-induced cardiovascular collapse was recently published. Out of the total of 9 cases included, one was exposed to lamotrigine in association with duloxetine and verapamil. The authors suggest the administration of ILE for the treatment of refractory cardiovascular collapse; however, its use should be restricted to cardiac arrest or refractory shock [16].

This case demonstrates the potential cardiac and neurologic severity of intoxication with lamotrigine alone, while the majority of lamotrigine overdoses reported in the literature have had a relatively benign course and have been associated with a co-ingestant [5]. In contrast to previously published cases, the QRS complex prolongation was associated with a right bundle branch block, and this did not change after the administration of sodium bicarbonate. The resolution of the electrocardiographic changes was noted immediately after the administration of ILE, suggesting a potential role for this therapeutic intervention as a mean to prevent the development of fatal arrhythmias.

Conclusion

Cardiac intraventricular conduction could be delayed in some cases of lamotrigine overdose, resulting in electrocardiographic changes suggestive of sodium channel blockade. These changes include QRS and QTc prolongation and R wave >3 mm in leads I and aVR. Intravenous lipid emulsion has been successfully used in the treatment of lamotrigine cardiac toxicity refractory to sodium bicarbonate.

Conflict of interest The authors declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this article.

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