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Case Report

Low-dose lacosamide-induced atrial fibrillation: Case analysis with literature review☆,☆☆

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ABSTRACT

Lacosamide (LCM) is a novel antiepileptic drug (AED) approved by the FDA for adjunctive treatment of partial epilepsy with and without secondary generalization. Lacosamide dose-dependent dysrhythmias (PR-interval prolongation, AV block, and atrial fibrillation/flutter) have been reported. This case represents the first instance of LCM-induced atrial fibrillation following a low loading dose (200 mg). Risk factors for atrial fibrillation are addressed and discussed in the context of this case. Full cardiac history is recommended prior to patients being initiated on LCM. Cardiac monitoring may be required for at-risk patients on LCM. Clinicians need to be cognizant of this potential adverse effect.

1. Introduction

Lacosamide (LCM) is a novel antiepileptic drug (AED) approved by the U.S. Food and Drug Administration (FDA) for the adjunct treatment of partial epilepsy with and without secondary generalization [1]. Lacosamide selectively modulates voltage-gated sodium channels by enhancing slow inactivation without affecting fast inactivation to exert its antiepileptic activity [1–3]. Lacosamide has linear pharmacokinetics, reaches maximum concentration within 1–4 h following oral administration, and has a half-life of 13 h [2]. Lacosamide is a potent antiepileptic agent with superior efficacy compared to placebo in patients with partial seizures [4,5]. The choice of AED is related to both its efficacy in treating seizures and its side-effect profile.

Dose-dependent LCM-induced cardiac dysrhythmias have been reported in recent literature [4,6–9]. High-dose LCM (600 mg total daily dose) has been associated with atrial fibrillation/flutter. The authors report a case believed to represent the first instance of low-dose LCM-induced atrial fibrillation.

2. Method

Case analysis was done with PubMed literature review.

3. Case report

A 67-year-old right-handed woman with history of epilepsy, migraines, and recently diagnosed plasma cell multiple myeloma with lambda-free light chains and with swollen tongue presented to our institution for autologous bone marrow transplant. There was no known history of structural heart disease or conduction abnormalities though a family history (mother/brother) of atrial fibrillation was later determined. One week following the bone marrow transplant, frequent episodes of staring associated with oral and facial automatisms (lip smacking and head shaking) were noted which prompted neurology consultation.

Medications at time of consultation included primidone 250 mg daily, fluconazole 400 mg daily, acyclovir 400 mg every 12 h, filgrastim 300 μg daily, methyl-prednisolone 40 mg IV daily, pantoprazole 40 mg daily, potassium chloride, and clotrimazole mouthwash 10 mg five times a day which she did not receive that day due to epigastric discomfort. The patient had received loperamide 10 mg 3 times in the last 2 days and ondansetron 8 mg IV on the day prior to consultation.

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Comprehensive metabolic panel and complete blood count were normal on the day of consultation excluding sodium 134 mEq/L, fasting glucose 108 mg/dL, hemoglobin 8.5 g/dL, and hematocrit 24.5%. Phenobarbital level was 3.6 μg/mL. Her ECG revealed a sinus rhythm at 96 bpm with premature ventricular contractions with QTc of 437 ms and PR of 156 ms.

During this consultation, the patient revealed a history of three generalized tonic-clonic (GTC) seizures at age 21 associated with an aura described as tinnitus. The convulsive seizure activity responded to primidone 250 mg total daily dose; however, the patient reported ongoing tinnitus occurring once monthly and had been told by her family that she would have brief periods of behavioral arrest with staring, which she minimized by stating that she was thinking of a response.

Initial routine EEG revealed 1) disorganized background characterized by diffuse slowing with frontally predominant theta and delta activities and intermittent semi-rhythmic delta activity; 2) intermittent left fronto-temporal polymorphic delta activity; and 3) few left fronto-temporal high-amplitude sharp waves (Fig. 1). Clinical presentation and EEG were consistent with partial epilepsy with left temporal region complex partial seizures.

Following initial evaluation by the neurology team, levetiracetam 250 mg IV twice daily was initiated without significant change in clinical status. Intravenous administration was required as the patient was not tolerating oral medications and had vomited her primidone.

Her episodes increased in frequency with descriptive features including continuous tinnitus, staring, facial automatisms, limited verbal responses and lethargy. Levetiracetam was titrated to 500 mg IV twice daily with primidone 300 mg daily, and the patient was placed on continuous video-EEG (vEEG) to better characterize seizure activity and to monitor treatment response. During a four-hour period on continuous vEEG, greater than 30 episodes were recorded with electrographic correlation including seizures with and without secondary generalization (Fig. 2). The patient had continued lethargy with altered mental status between episodes consistent with complex partial status epilepticus. Immediate treatment with lorazepam 2 mg IV bolus was ineffective. Levetiracetam was increased to 1000 mg twice daily, and the patient received a loading dose of lacosamide 200 mg IV given over 60 min.

The patient was noted to have an irregular cardiac rhythm on the vEEG telemetry lead at the end of the lacosamide infusion (Fig. 3). A 12-lead ECG confirmed atrial fibrillation with rapid ventricular response (132 bpm). Cardiac telemetry was initiated and continued until the patient was discharged. Cardiology was consulted for this new-onset atrial fibrillation. At time of cardiac consultation, the patient's comprehensive metabolic panel and complete blood count were normal excluding sodium 128 mEq/L, potassium 3.4 mEq/L, glucose 142 mg/dL, phosphorus 2.1 mg/dL, white blood cell count 0.1 thousand/μL, red blood cell count 2.4 million/μL, hemoglobin 7.3 g/dL, hematocrit 21%, and platelet count 45 thousand/μL. Pertinent normal laboratories included troponin I<0.03 ng/mL, magnesium 1.8 mg/dL, and TSH 1.56 mIU/L. Lacosamide was discontinued following the infusion and the atrial fibrillation, which did not respond to metoprolol 2.5 mg IV, spontaneously resolved within 8 h. A trans-thoracic echocardiogram (TTE) was performed on the following day and revealed a normal left ventricular size and systolic function with an estimated ejection fraction of 55%, a normal right ventricular size and systolic function, normal bi-atrial size, mild aortic insufficiency, and mild tricuspid regurgitation with moderate pulmonary hypertension (right ventricular systolic pressure of 59 mm Hg). A subsequent TTE confirmed these findings. Cardiology concluded that the atrial fibrillation was induced by the lacosamide infusion as there were no structural or motion abnormalities.

Anticonvulsant regimen was changed to levetiracetam 1500 mg IV twice daily and, following two boluses of phenobarbital 600 mg IV, phenobarbital 60 mg IV every 8 h without significant change in seizure frequency. Video-EEG showed a seizure frequency of 6 to 8 events per hour, each lasting approximately 60 s in duration, consisting of left temporal rhythmic sharp waves with staring. The patient received phenytoin 1200 mg IV loading dose following which the vEEG recorded a three-hour seizure-free period without epileptiform activity; thereafter, the patient remained seizure-free though intermittent sharp waves were noted. Levetiracetam was discontinued, and seizure freedom persisted with phenobarbital 60 mg IV every eight hours and phenytoin 100 mg IV every eight hours with respective anticonvulsant blood levels of 23.9 μg/mL and 2.1 μg/mL (free).

Ninety-six hours after the initial atrial fibrillation, the patient had another brief period of atrial fibrillation that lasted several minutes without any clinical complication. A full 48 h without seizure activity

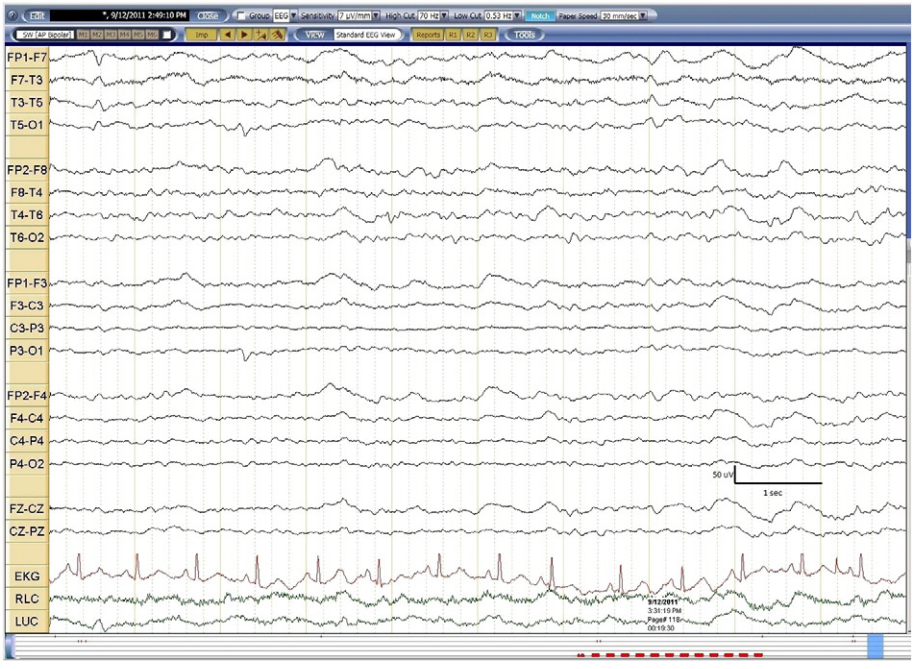

Fig. 1. Initial routine EEG.

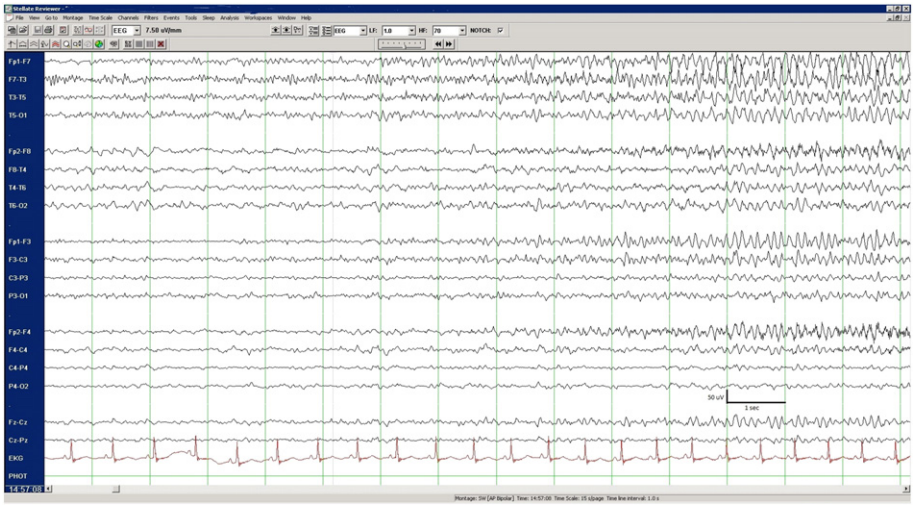

Fig. 2. Seizure activity with sinus rhythm pre-lacosamide infusion.

was recorded, and vEEG was discontinued. The patient remained on cardiac telemetry during the remaining two weeks of her admission during which time there were no further episodes of atrial fibrillation. Upon discharge, the patient returned to her primary care neurologist.

4. Discussion

This unique case of apparent low-dose lacosamide-induced atrial fibrillation in a patient with refractory epilepsy and nonconvulsive complex partial status epilepticus allows the discussion of several key points both specific to this patient and to the LCM treatment of patients considered to be at high risk for cardiac dysrhythmias.

First, patients often minimize their symptoms in acute and chronic medical conditions as well as adverse drug reactions which may lead to increased morbidity and mortality [10–12]. In this instance, minimizing symptoms led to untreated complex partial seizures; for though her tonic-clonic seizures were controlled with primidone, the patient had ongoing periods of tinnitus with behavioral arrest and staring. Minimizing these epileptic symptoms led to an unnecessary treatment gap.

Second, several adverse cardiac events have been reported with LCM. Events include dose-dependent PR-interval prolongation, first-, second- and third-degree AV blocks, and atrial fibrillation/atrial flutter with high-dose LCM (600 mg/day) [4,6–9,13,14].

Third, current clinical practice and recent literature suggest that LCM may be used in older and critically ill patients [15–17]. This patient population is at greater risk for atrial fibrillation as the reported risk factors for atrial fibrillation include, but are not limited to, older age, male gender, hypertension, diabetes, congestive heart failure, myocardial infarction, cardiac surgery, valvular disease, severe sepsis, hyperthyroidism, obesity, and smoking [18–21]. Older age was a risk factor in this case.

Fourth, cardiac amyloidosis is a risk factor for atrial fibrillation [22]. The patient had a swollen tongue at admission and post hospitalization laboratories confirmed amyloid. These findings are consistent with presumptive amyloidosis. Though the echocardiogram was normal, a cardiac biopsy was not performed, and as such, early cardiac amyloidosis could not be excluded. Therefore, cardiac amyloidosis may have been a risk factor in this case.

Fifth, analysis of the Framingham Offspring Study noted that parental atrial fibrillation is associated with a 1.85 odds ratio for atrial fibrillation in the offspring [23]. In this case, both the patient's mother

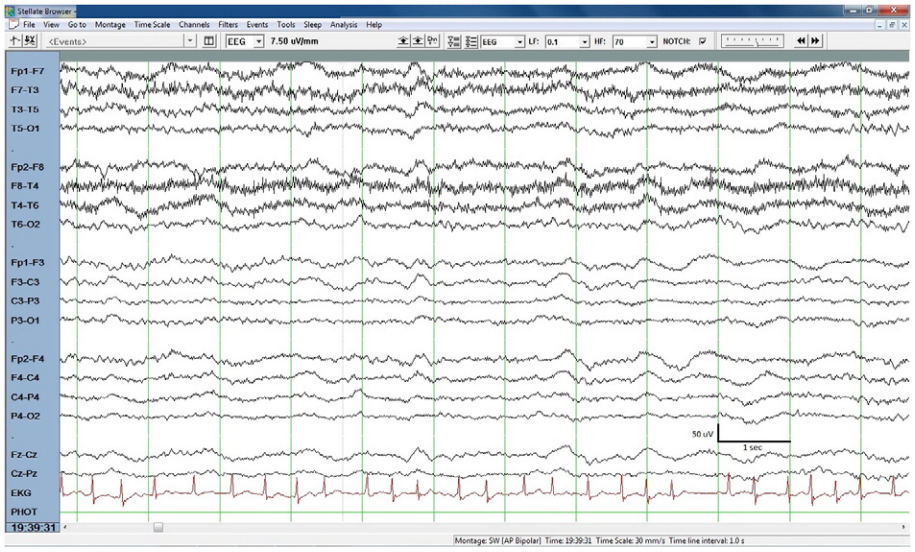

Fig. 3. Atrial fibrillation post-lacosamide infusion.

and brother had atrial fibrillation. Genetic predisposition was a risk factor in this case [19].

Sixth, the patient's second period of atrial fibrillation, lasting several minutes 96 h after the LCM-associated atrial fibrillation, may imply unknown cardiac pathology as a predisposing risk factor.

Seventh, atrial fibrillation occurred at the end of the LCM IV infusion, consistent with the theoretical maximum blood concentration [14]. Lacosamide has linear (first-order) pharmacokinetics with an elimination half-life of 13 h [2,24]. The spontaneous resolution of atrial fibrillation within 8 h following the LCM infusion suggests a concentration-dependent effect.

Eighth, the patient had multiple potential risk factors (older age, possible cardiac amyloidosis, genetic predisposition, and possible unknown cardiac pathology) for cardiac arrhythmias. In the context of additive risk factors, the probability of LCM inducing the initial episode of atrial fibrillation was determined by the Naranjo's Adverse Reaction Probability Scale as probable (scored as 5) [25].

Ninth, as LCM may cause (or precipitate) cardiac dysrhythmias including atrial fibrillation in susceptible patients, recommendations prior to the initiation of LCM may include 1) obtaining baseline 12-lead ECG, 2) obtaining careful cardiac history verifying potential risk factors including family history of atrial fibrillation or other dysrhythmias, 3) obtaining comprehensive metabolic panel with magnesium, 4) normalizing electrolyte levels, and 5) adjusting LCM dose based on renal and hepatic functions. Further, as this paper suggests that LCM-induced atrial fibrillation may occur at low doses cardiac monitoring during both initial LCM administration and titration should be considered.

There are specific limitations to this paper. As a case report ($N = 1$), the findings cannot be generalized. In this case, and other studies of atrial fibrillation, pre-existing asymptomatic atrial fibrillation cannot be excluded. Lacosamide blood level was not measured. Cardiac biopsy to confirm amyloidosis impacting the heart was not obtained. Though the patient had a family history of atrial fibrillation, no genetic assessment was performed to confirm familial atrial fibrillation. The patient was lost to clinical follow-up. Finally, the patient could not be re-challenged with lacosamide for ethical reasons.

5. Conclusion

Low-dose lacosamide may induce atrial fibrillation, especially in patients at risk for cardiac arrhythmias. Clinicians need to be aware of this potential adverse drug effect and to evaluate and monitor at-risk patients appropriately. Further research is indicated to confirm this finding.

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