The Safety of Lacosamide for Treatment of Seizures and Seizure Prophylaxis in Adult Hospitalized Patients

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Abstract

Background: Lacosamide (LCM) is a newer antiepileptic drug (AED) with favorable properties for hospitalized patients including intravenous formulation, minimal hepatic metabolism, and no adverse respiratory effects. We sought to determine the safety profile of LCM in hospitalized patients. **Methods:** We performed a retrospective medical record review of patients who received LCM between July 1, 2009, and January 31, 2010, at Mayo Clinic Hospital. Data included demographics, LCM dosing, concomitant AED therapy, documented seizure activity, hemodynamic variables, electrocardiogram (ECG), and laboratory data. Adverse drug reaction and drug–drug interactions were reviewed. **Results:** Thirty-two patients were identified. No major hypotension or serious cardiac arrhythmias occurred. Heart rate increased, however, in seizure group compared with the prophylaxis group 2 hours postdrug infusion (median heart rate = 86 vs 164). The ECGs demonstrated a mean PR interval prolongation of about 6 milliseconds (ms) after LCM initiation (mean PR 185.5 ms, compared with baseline ECG mean of 179.3 ms). Laboratory data revealed no clinically significant changes 24 hours after LCM initiation. Three patients developed adverse events (9.4%): One with altered mental state and exceptionally prolonged ECG PR interval (212 vs 178 ms baseline); One with unexplained thrombocytopenia; and a third patient with dizziness, all of which resolved after drug discontinuation. **Conclusion:** The LCM demonstrated ECG PR prolongation as previously reported without systemic hypotension, with no discernable drug–drug interactions in hospitalized patients. About 9% of patients had transient adverse drug reactions after LCM, namely alteration in mental state, unexplained thrombocytopenia, and dizziness, which stopped after discontinuation of the drug.

Keywords

seizures, epilepsy, status epilepticus, epilepsy, antiepileptic drugs

Introduction

Despite advances in antiepileptic therapy, some patients remain refractory to treatment or unable to tolerate therapy. It is estimated that epilepsy affects more than 50 million people worldwide with up to 30% of patients failing to maintain remission.¹ Seizures and status epilepticus (SE) in critically ill patients require aggressive treatment and early intervention.^{2,3} An ideal intravenous (IV) anticonvulsant facilitates access to the brain, while posing little risk of serious systemic and neurological adverse effects—traits necessary for patients in neurocritical care settings.⁴ Antiepileptic drugs (AEDs) commonly used in emergent cases may complicate therapy by prompting the need for mechanical ventilation, IV fluids, vasopressors, and electroencephalogram (EEG) monitoring. Treatment may be limited by cardiac or respiratory depression and unwanted hemodynamic effects as seen with phenytoin, benzodiazepines, and barbiturates.^{2,5,6}

Lacosamide (LCM; Vimpat, Smyrna, Georgia) is a novel AED that was approved by the Food and Drug Administration (FDA) in October 2008 for adjunctive therapy of partial-onset seizures. It is the first in its class with a dual mechanism of action, involving selective enhancement of sodium channel slow inactivation and collapsin response mediator protein 2 (CRMP-2) modulation.⁷ It is proposed to mediate neuronal

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Table 1. Baseline Characteristics of Patients Who Received LCM for Seizure Prophylaxis or Seizure Treatment^a

Characteristic	Seizure Prophylaxis (n = 12)	Seizure Treatment (n = 20)
Age (range), years	79 (18; 28-90)	47 (20.8; 18-79)
Male (%)	6 (50)	11 (55)
SCr, mg/dL	0.8 (0.7-1.2)	0.8 (0.7-1.2)
BUN	17 (12.5-29.1)	14 (12.4-20.5)
AST	29 (12.1-59.9)	21 (11.4-64.7)
ALT	16 (-17.4-72.9)	30.5 (16.9-67.5)
Alk Phos	70 (38.8-110)	83 (44.5-62.5)

Abbreviations: LCM, lacosamide; SCr, serum creatinine; ALT, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Alk phos, alkaline phosphatase.

^aAge is presented as mean (standard deviation; range); continuous data are presented as median (95% CI); categorical data are presented as number of patients (percentage of sample).

hyperexcitability by normalizing activation thresholds with decreased pathophysiological neuronal activity through effects on the sodium channels.^{7,8} The CRMP-2 modulation, as part of the signal transduction cascade of neurotrophic factors, may contribute to potential antiepileptogenic effects and decreased neuronal loss observed in SE animal models.⁷⁻⁹ To date, little research has been conducted regarding the usage of LCM in acute care settings. We retrospectively analyzed the safety and use of LCM in hospitalized adult patients for seizure prophylaxis or treatment of active seizures.

Methods

A retrospective study was performed after approval by the Mayo Clinic Institutional Review Board, by reviewing the electronic medical record of all patients admitted to the single academic medical center (Mayo Clinic Jacksonville, Florida) from July 1, 2009, to January 31, 2010, who received LCM as adjunctive or monotherapy for seizure prophylaxis or treatment as determined by clinical diagnosis or EEG in the hospital setting. The primary objective of this study was to review the safety of LCM for seizure prophylaxis and active seizure treatment in hospitalized patients. Data collection included heart rate, systolic blood pressure, diastolic blood pressure, serum creatinine (SCr), liver function tests (LFTs), mean PR interval, adverse reactions, and drug interactions. Additional data collected included age, sex, indications for drug therapy, dosing regimen, the primary medical service such as intensive care unit (ICU) or ward floor, and other concomitant AED treatment. Patients were excluded from the study if they were younger than 18 years of age or had a known allergy to LCM.

Results

We identified 32 patients treated with LCM during the study period (17 males; mean (standard deviation [SD]; range) age,

Table 2. Hemodynamic Parameters of Patients Who Received LCM for Seizure Prophylaxis or Treatment^a

Characteristic	Seizure Prophylaxis (n = 12), median (95% CI) ^a	Seizure Treatment (n = 20), median (95% CI) ^a
2 hours prior LCM		
HR, bpm	87.5 (74.1-100.9)	92 (83.2-100.7)
SBP, mm Hg	129 (119.2-138.8)	148 (140.6-155.4)
DBP, mm Hg	69 (61.5-76.5)	69 (65-72.9)
2 hours post LCM		
HR, bpm	86.5 (76.7-96.3)	164 (152.4-175.6)
SBP, mm Hg	131.5 (117.2-145.8)	169 (158.8-179.2)
DBP, mm Hg	61 (51.9-70)	81 (75-86.9)
4 hours post LCM		
HR, bpm	78.5 (68.2-88.7)	103 (94.4-111.6)
SBP, mm Hg	126 (113.2-138.7)	143 (133.5-152.5)
DBP, mm Hg	65 (56.1-73.8)	66 (59.2-72.7)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

^a Continuous data presented as median values and 95% CI in parenthesis.

56.8 (23.8; 18-90) years). Of those patients, 17 were admitted to the medical or surgical ICU. Patients were categorized into 2 groups for analysis; 12 patients received LCM for seizure prophylaxis and 20 patients received LCM for acute seizures or SE. Baseline characteristics are summarized in Table 1; laboratory data revealed no clinically significant changes in baseline and 24-hour postdrug SCr or LFTs. Three patients receiving seizure prophylaxis (3 of 12; 25%) and 4 patients treated for active seizures (4 of 20; 20%) had a reported seizure after LCM initiation per clinical documentation.

No serious cardiac arrhythmias and cardiac or respiratory arrest occurred in any patient who received LCM. Hemodynamic parameters are summarized in Table 2. Regarding hemodynamic instability, we noted an increase in heart rate 2 hours postinfusion as shown in Table 2, but note that in the ICU setting, there are numerous causes of increased heart rate including pain and other stimuli. Laboratory data revealed no clinically significant changes prior and post-LCM administration. Electrocardiograms (ECGs) in selected patients demonstrated a mean (SD; range) PR interval of 185.5 ms (33.1; range 148-254) postdrug initiation compared with a baseline of 179.3 ms (47.5; range 80-274).

A majority of seizure patients (20/32; 62.5%) received LCM as adjunctive therapy, whereas 12 patients (12 of 32; 37.5%) received monotherapy. No known drug interactions were identified during this study. Several patients received agents requiring therapeutic drug level monitoring, including carbamazepine, phenobarbital, valproic acid, and phenytoin. Levels were not routinely ordered for all patients in these other anticonvulsants. However, the drug levels of 3 patients on phenytoin and 1 patient on phenobarbital remained therapeutic after LCM initiation.

Adverse events following LCM administration were reported in 3 patients (3 of 32; 9.4%). A patient receiving levetiracetam and LCM for seizure treatment experienced agitation, altered mental status, and PR interval prolongation (212 vs 178 ms baseline). The patient received 3 doses of LCM before both agents were discontinued. One patient developed thrombocytopenia of unknown etiology while receiving LCM treatment. A total of 13 doses were given prior to discontinuation, upon which the thrombocytopenia resolved. Another patient developed dizziness and nausea with outpatient treatment of LCM after receiving 9 doses of inpatient therapy. Despite decreasing the maintenance dose, there was no resolution of adverse effects and LCM was discontinued due to intolerance.

Reasons for seizure prophylaxis primarily included perioperative aneurysmal clipping and coiling (4 of 12; 33.3%), subarachnoid hemorrhage (4 of 12; 33.3%), and postcraniotomy (3 of 12; 25%). The rationale for LCM monotherapy was based on the treating physician's discretion for a "nonsedating" AED, or intolerance to levetiracetam or other AED. Characterization of LCM use or indication is summarized as follows: patients requiring treatment for active seizures most commonly received LCM for refractory seizures (8 of 20; 40%), SE (3 of 20; 15%) and seizures secondary to brain tumor (2 of 20; 10%). Patients mainly received care from neurology, neurosurgery, and critical care services; however, the seizure treatment group included patients followed by heart ($n = 1$) and liver ($n = 1$) transplant services. All patients initiated on LCM for seizure prophylaxis ($n = 12$) were administered the first dose in the ICU compared with 9 patients (9 of 20; 45%) receiving seizure treatment. A majority of patients (22 of 32; 68.7%) received a loading dose, with 200 mg as the most commonly administered dose, which was infused at least over 30-minute period. The most common maintenance dose was 100 mg twice daily (22 of 32; 68.7%). Nineteen patients first received LCM in the IV formulation before receiving it orally; 6 patients received the IV formulation only, while 7 patients received LCM by oral route only. Duration of inpatient therapy was similar between both groups, with a mean (SD; range) duration of therapy of 11.7 (21.1; 115-2) days. The LCM was prescribed at discharge for a majority of patients (19 of 32; 59.4%).

Discussion

Seizures in hospitalized and critically ill patients often occur from various or "provoked" seizure risk factors, such as a lowered seizure threshold in systemic infection, fever, sleep deprivation, severe electrolyte derangements, or acute brain insults such as stroke which require early intervention^{2,3} for improved outcomes. The development of an anticonvulsant with minimal hemodynamic effects and minimal depression on the patient's level of consciousness would be ideal for hospitalized patients. The LCM is a newer anticonvulsant with minimal hemodynamic depression and drug-drug

interactions, with subclinical ECG PR prolongation.⁶⁻⁹ However, data regarding hospitalized patients and LCM use remain largely under reported.^{10,11}

Kellinghaus et al, for example, details the use of IV LCM as successful treatment for a single patient with nonconvulsive SE after failure of lorazepam as first-line therapy.¹⁰ Older anticonvulsants such as barbiturates and phenytoin, while effective, have concern for potential sedation, cardiac depression,⁵ and drug-drug interactions. Valproic acid and levetiracetam have minimal depression in the level of consciousness and hemodynamics. Valproate is also FDA approved for primary or secondary (adjunctive) anticonvulsant medication use. However, valproic acid has several potential adverse reactions or side effects including neural tube defects in pregnant females, weight gain, hirsutism (especially females with polycystic ovarian syndrome), tremor, elevation of liver/pancreatic function tests, and thrombocytopenia. Levetiracetam has negligible protein-binding and hepatic metabolism and therefore has minimal drug-drug interactions, however, it is FDA approved for adjunctive AED management. The LCM also has a favorable pharmacokinetic profile and is FDA approved for adjunctive use in patients with partial seizures.¹² The ideal anticonvulsant would therefore have both IV and PO (enteral) 1:1 conversion and could be used in emergent situations, with no adverse hemodynamic or respiratory effects and no monitoring of drug levels.

The ideal anticonvulsant would be with a single drug or "monotherapy," unless seizure control cannot be attained or adverse effects prompt the addition of a second agent.¹¹ The addition of more than 1 anticonvulsant to medically complex patients increases the risk of adverse events and drug-drug interactions especially with older AED or in difficulty in maintaining therapeutic levels by alterations in drug metabolism.⁴ The AED agents such as phenytoin, phenobarbital, and valproic acid are strongly protein bound, with the unbound portion active in the patient serum. In hospitalized and critically ill patients, serum proteins are often altered due to the elevation in acute phase reactants and lower serum albumin, which results in significantly higher "free" drug concentrations.^{3,4} The LCM may prove to be advantageous in such patients due to less than 15% protein binding with low risk of displacement by drug-drug interactions.^{9,13-15} Additionally, LCM does not cause induction or inhibition of CYP450 isoenzymes with minimal hepatic metabolism. Drug interaction studies have shown no effect of LCM on the pharmacokinetics of carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, valproic acid, metformin, digoxin, omeprazole, or oral contraceptives (ethinyl estradiol/levonorgestrel).^{9,13-15} Conversely, a study with healthy volunteers showed that plasma concentrations of LCM were not affected by concomitant therapy with carbamazepine and valproic acid despite their known CYP450 induction and inhibiting effects.⁷ The LCM does require dose adjustments in patients with hepatic and renal dysfunction, which may be a frequent occurrence in the more critically ill population.

Common adverse events reported in a study by Ben-Menachem et al⁷ evaluating LCM were central nervous system and gastrointestinal events such as dizziness, headache, nausea, fatigue, ataxia, vision abnormal, diplopia, vertigo, and nystagmus. There was also a small dose-related increase in mean PR interval with no indication of QT/QTc prolongation after evaluation of ECG data. The study by Biton et al¹⁶ reported similar adverse effects including dizziness, headache, injection site pain, somnolence, and a small increase in mean PR interval. A complete review of AED drug side effects is outside the scope of this article, a comprehensive review by Tatum is noted within the last year among various AED and side effects.¹⁷

Adult hospitalized patients were evaluated in this study, which we feel are an important and underreported group of patients for this new anticonvulsant, with minimal data regarding its safety. Our patients received LCM for acute seizure management primarily, refractory, recurrent seizure management (8 of 20; 40%), or SE (3 of 20; 15%) with other AEDs. While the current study was not designed to review efficacy, we observed that 75% of patients (n = 9) receiving LCM for seizure prophylaxis and 80% of patients (n = 16) treated with LCM for active seizures did not have a subsequent seizure. Laboratory data revealed no clinically significant changes in baseline and 24-hour postdrug SCr or LFTs. No hemodynamic instability, serious cardiac arrhythmias, nor cardiac or respiratory arrest occurred in any patient who received LCM. The majority of seizure patients (20 of 32; 62.5%) received LCM as adjunctive therapy. Two solid organ transplant patients (heart, n = 1; liver, n = 1) were included. Transplant recipients are often vulnerable to the consequences of drug–drug interactions due to immunosuppressive drug levels and complex medication regimens. No drug interactions or alteration in cyclosporine or tacrolimus levels were identified during the entire hospitalization in these 2 patients receiving LCM.

Adverse events in this patient population are important to note and included 3 (~9%) patients. One patient had agitation, altered mental status, and PR interval prolongation. We did observe a transient increase in the post 2-hour post-LCS infusion heart rate for those in the active seizure treatment group. This is likely a multifactorial response including a post-seizure hypersympathetic effect, postictal confusion, pain, critical illness, and perhaps other technical aspects of measurement not otherwise evident. We cannot exclude the drug as causing this effect, but it was not present in the “seizure prophylaxis group” (Table 2). We have no other physiological explanation for this and cannot attribute to the drug since it was not observed with infusion in the prophylaxis group. Regarding the patient who developed unexplained thrombocytopenia, there was no other apparent cause other than LCM use, which resolved upon discontinuing the drug. Thrombocytopenia is not a reported side effect of LCM, and we find this a potentially important observation due to the observance of thrombocytopenia in 1 patient in the study. Finally, 1 patient

developed “dizziness and nausea” despite a reduction in maintenance dose, with no resolution of intolerance. These symptoms stopped when the drug was eventually discontinued.

There are several limitations to this study, including the retrospective design and lack of control group. However, we feel the strength of the current study is that it is one of the largest reported series of LCM used in hospitalized and critically ill patients to date.¹⁸ The data also have clinical relevance to practitioners about the inpatient safety profile of LCM in hospitalized patients, which to date has been underreported. We observed an increase in heart rate 2 hours postinfusion of the drug in the patients who had a seizure, which could be related to the seizure itself (hypersympathetic activity), postictal autonomic changes, or the drug, but this was not seen in the seizure prophylaxis group.¹⁹

Conclusion

The vast majority of hospitalized patients receiving 100 to 200 mg of LCM as a loading dose tolerated the drug well, with no adverse effects on SCr or LFTs. No hypotension, serious cardiac arrhythmias, and cardiac or respiratory arrest occurred in any patient, but in the seizure treatment group, an increase in heart rate was noted. The ECG PR prolongation was observed to be similar to the drug’s package insert, especially with higher and rapid dosing. Three patients (3 of 32; 9.4%) experienced adverse events while receiving LCM, all of which resolved upon drug discontinuation. Prospective, randomized studies should evaluate LCM as a primary anticonvulsant in hospitalized patients for acute seizure management as its properties may provide an alternative for seizure management especially in complex medical or transplant patients with multiple comorbidities and medications. The LCM should be used with caution in patients with unstable cardiac condition or where prolongation of the PR is unsafe and with renal impairment.

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Declaration of Conflicting Interests

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