Clinical Neurology and Neurosurgery 171 (2018) 179–183

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Lacosamide efficacy and tolerability in clinical practice – Post marketing analysis from a single dedicated epilepsy center

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ARTICLE INFO

Keywords:
Lacosamide
Efficacy
Tolerability
Post-marketing
Analysis

ABSTRACT

Objectives: Post marketing analysis of anti-epileptic drug (AED) efficacy and tolerability is of great value to the clinician since it is more representative of clinical practice than clinical trial data. We analyzed our experience with lacosamide (LCM) in patients treated after marketing.

Patients and methods: We identified all patients who were treated with LCM during the four year period after marketing, excluding patients who were in clinical trials. We recorded demographic data and analyzed efficacy and tolerability in patients who had at least one follow up visit or telephone call 3 months after the initiation of LCM.

Results: A total of 165 patients met our inclusion criteria. The mean age was 41 years. The majority of the cohort had focal epilepsy (146 patients) (88.4%). The mean duration of treatment was 31.2 months. Eighty one patients (49.1%) were continuing LCM at last follow up. Adverse effects (AEs) and discontinuation were significantly more common when LCM was added to one or more Na-channel blocking agents (NCB) ($p = 0.0003$ and 0.17). The 50% responder rate was 26% at 3 months and increased to 49% at 36 months. Patients were more likely to continue the drug and less likely to have AEs with slower titration over ≥ 4 weeks ($p = 0.02$ for each). Four or more previously failed AEDs predicted poorer response rate compared to three or less AEDs ($p = 0.001$).

Conclusion: LCM use in clinical practice was associated with greater rate of seizure freedom than in clinical trials. Discontinuation and occurrence of AEs were significantly more likely with faster titration and adding LCM to NCB agents.

1. Introduction

Epilepsy is a common neurological disorder with a cumulative incidence of 3.1% through age 74 years [1]. This corresponds to about 50 million people worldwide. There are between 16–51 cases of new-onset epilepsy per 100,000 people every year [2]. Approximately 35% of epilepsy patients have poor response to medical management and prove to be drug resistant [3–5]. There are other potential palliative and curative treatment options for this group of patients. These include resective epilepsy surgery, vagal nerve stimulation, responsive neurostimulation or dietary measures. However a good percentage of refractory patients will not qualify for or respond to the non-medical treatment modalities and still rely on medical management alone. Only a small additional portion of refractory patients (3%) will achieve seizure freedom with continued medical management [5]. Lack of seizure freedom will often result in comorbidities such as depression and increased AED burden affecting the quality of life negatively [6]. Within the last decade several reports challenged the definition of drug resistant epilepsy and indicated that up to 15–16% of drug resistant patients could become seizure free with medical management alone over a three-year period [7–9]. This emphasized the importance of pursuing the search for new AEDs, most effective doses and combinations. While we often depend on clinical trial data for treatment decisions, these data may not be representative of everyday clinical practice. Post marketing analysis could help clinicians better understand efficacy and tolerability in a diverse group of patients with different types of seizures and comorbidities. We therefore reviewed all patients who were treated with lacosamide (LCM) in a tertiary care center in an effort to characterize LCM's long term effectiveness and tolerability in a retrospective cohort of adult patients.

LCM (2-acetamido-*N*-benzyl-3-methoxypropionamide) is a new AED marketed in the United States of America since 2009. LCM's efficacy with focal seizures is confirmed in several previous placebo-controlled trials with > 50% reduction in seizure frequency in up to 50% adults

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https://doi.org/10.1016/j.clineuro.2018.06.022
Received 23 January 2018; Received in revised form 11 June 2018; Accepted 12 June 2018
Available online 13 June 2018
0303-8467/

[10–13]. During the pivotal trials doses of 200, 400 and 600 mg per day were tried. While the most effective dose was 600 mg per day the discontinuation rate was also highest at 30% at this dose. The leading cause of drug discontinuation as well as the most frequent side effects was dizziness [13–15].

LCM has two proposed novel mechanisms of action. The first is through its enhancement of slow inactivation of voltage gated sodium channels (VGSC). After depolarization and sodium ion influx across neuronal cell membranes, VGSCs enter an inactivated state before they are ready for another depolarization. During the inactivated state, VGSCs are unavailable for depolarization. This is the fast inactivation which is milliseconds long and the traditional sodium-channel blocking AEDs exert their effect by acting on this site. Slow inactivation usually occur with sustained depolarization and needs a conformational change. This inactive state is seconds long. LCM enhances this slow inactivated state, reducing the availability of VGSCs for depolarization and subsequent neuronal firing [16,17].

The second potential mechanism of action is its binding to collapsin response mediator protein 2 (CRMP-2), which is involved in neuronal differentiation, polarization, and axonal outgrowth. To date, the exact effects of the interaction of LCM and CRMP-2 on seizure control have not been determined [16–18]. A recent pre-clinical study documented that LCM might also act on GABA currents decreasing use-dependent decrease (run-down) of the GABA elicited inward currents (I_{GABA}) which is a hallmark of refractory epilepsy. This could have future potential clinical implications [19,20].

2. Materials and methods

Medical records of all patients started on LCM for epilepsy were retrospectively reviewed during the four year period after marketing. Patients were identified from adult epilepsy clinic panels of five academic epileptologists working at Vanderbilt University Medical Center. We included patients over 16 years of age, with epilepsy or new onset seizures. Patients previously enrolled in LCM trials and with psychogenic seizures including the ones who had co-existing epilepsy were excluded. We also excluded patients who were started on LCM for reasons other than epilepsy. Seizure classification was made by recorded typical events/seizures in epilepsy monitoring unit (EMU). When seizures were not captured with long term monitoring interictal discharges, when unequivocally present, were used for seizure classification. The seizure classification of some patients were made through reliable history and seizure description or home recorded videos. We recorded demographics, seizure and epilepsy classification, age of seizure onset, etiologic factors, number of previously tried AEDs, seizure lateralization and localization when focal, use of rescue medications, baseline AEDs, seizure frequency at baseline during the 3 months before treatment, seizure frequency after treatment at 3, 6, 12, 24 and 36 months, duration of titration for LCM, adverse experiences, and the reason for discontinuation for those who stopped LCM. Presence of adjunctive Na-channel blocking AEDs (NCBs) (lamotrigine, carbamazepine, oxcarbazepine, and phenytoin) were separately analyzed for their effect on tolerability and efficacy as compared to non-NCBs. All patients were asked to keep a seizure diary. Efficacy analysis was made in patients who returned for follow up with at least three months of LCM treatment. Tolerability analysis was possible for all treated patients who had at least one follow up visit or telephone call. All patients who qualified for inclusion criteria were included in efficacy and tolerability analysis. Tolerability was recorded for the speed of titration and for final maintenance dose. Patients with subjective events only, who had recorded typical events in EMU without EEG correlate or had normal interictal EEGs with uncertain clinical diagnoses were excluded from our study. Change in seizure frequency was based on the 3, 6, 12, 24 and 36 months follow up appointments in comparison with baseline, as reported at the last clinic visit before starting LCM. We considered patients with ≥50% seizure reduction as responders, and ones with no seizures for the preceding six months as seizure free. We were not able to analyze LCM efficacy for specific seizure types for focal and generalized epilepsies. This was because clinicians did not consistently give the number of each specific seizure type during every patient visit. Instead we studied LCM efficacy in terms of change in overall seizure frequency. Response was classified as < 50% reduction, ≥50% reduction (responders), seizure freedom, and worsening of seizures.

The significance of parameters was calculated by chi-squared test and Fisher's exact test (two tailed). A value of $p < 0.05$ was considered as statistically significant. Our study and data collection methods were approved by the Vanderbilt institutional review board.

3. Results

3.1. Demographics

Inclusion criteria were met by 168 patients (101 female/67 male). One patient was excluded from the study due to being on LCM for neuropathic pain which was started by patient's general neurologist. Two additional patients who were initially started on LCM were also excluded since LCM was discontinued after their EMU admissions confirmed non-epileptic spells as the only event type. None of the remaining patients in our cohort had co-existing non-epileptic spells. The mean age for the remaining 165 patients was 41 years (SD: 12.8). The age range was 16–82.5 years; 154 (93%) patients were between ages 20 and 60 years. The mean age of seizure onset was 14.9 years (SD: 13.7). The average duration of epilepsy was 27.6 years. Epilepsy onset was in the first decade in 69 patients (41.5%) and in the first three decades in 142 patients (85.5%). Etiologic factors could be determined in 163 patients through history taking and brain imaging. This information was missing in medical records of two patients and these patients had also normal brain MRIs. Fifty seven patients had no known etiologic factors reported in history. The remaining patients had perinatal problems (prematurity/anoxia) (n = 10), febrile seizures (n = 16), head injury (n = 35), stroke (n = 5), CNS infections (n = 15), congenital malformations (heterotopia, cortical dysplasia) (n = 12) and other (n = 35). Twenty six patients had more than one etiologic factors. LCM was added on to one AED in 36 patients (21.8%), two AEDs in 67 patients (40.6%), and three or more AEDs in 60 patients (36.3%). Two (1.3%) patients were on LCM monotherapy. LCM was added to one or more NCBs in 126 patients. It was used as initiation monotherapy and conversion monotherapy in one patient each.

3.2. Seizure classification

The majority of the cohort had focal epilepsy 146 patients (88.4%); 13 (7.9%) had idiopathic generalized epilepsy, 4 (2.4%) had symptomatic (structural) generalized epilepsy and 2 (1.3%) had unclassified seizures (Table 1). In 132 patients seizure classifications were confirmed by recorded seizures in epilepsy monitoring unit (EMU). When EMU monitoring could not capture any seizures, unequivocally present interictal epileptiform activity with a reliable seizure history was used to determine the seizure classification (n = 21). Minority of the patients (n = 12) had their seizures classified through reliable history and medical records from referral sources. All patients in this latest group (n = 12) were referred from pediatric hospital and had structural epilepsy due to brain injury at birth or later in life. They were transferred to adult epilepsy clinic with established diagnosis of epilepsy therefore no EMU monitoring was done on these patients.

3.3. Dosing

The maintenance dose was ≤ 200 mg in 54 patients (32.7%), between 200–300 mg in 16 patients (9.7%), between 300–400 mg in 48 patients (29.2%) and ≥ 400 mg in 47 patients (28.4%). The final dose in 57 patients (34.5%) was reached after one week. In 41 of these