Seizure 20 (2011) 801–804

Contents lists available at ScienceDirect

Seizure

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

Early clinical experience with lacosamide as adjunctive therapy in patients with refractory focal epilepsy and nocturnal seizures

Irene García-Morales [a,b,*], Rafael Toledano Delgado [b], Mercé Falip [c], Dulce Campos [d], María Eugenia García [a], Antonio Gil-Nagel [b]

[a] Epilepsy Unit, Department of Neurology, Hospital Universitario Clínico San Carlos, Madrid, Spain
[b] Epilepsia Unit, Department of Neurology, Hospital Ruber Internacional, Madrid, Spain
[c] Epilepsia Unit, Department of Neurology, Hospital Universitari Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain
[d] Epilepsia Unit, Department of Neurology, Hospital Clínico Universitario, Valladolid, Spain

ARTICLE INFO

Article history:
Received 17 May 2011
Received in revised form 10 August 2011
Accepted 11 August 2011

Keywords:
Partial epilepsy
Lacosamide
Nocturnal seizures
Epilepsy treatment
Mood disorder

ABSTRACT

This retrospective study reports the early experience with lacosamide (LCM) as adjunctive therapy in Spanish patients with refractory focal epilepsy. Sixty patients (mean age 38.3 years, 54% women, mean epilepsy duration 27.2 years, mean seizure rate 9.7/month, and 28% with mainly nocturnal seizures) taking ≥2 antiepileptic drugs (mean 2.2) were included. LCM maintenance doses were 200, 300, 400, and 500 mg/day in 31, 16, 10, and 3 patients, respectively. Patients were followed up for 13–24 months. Twenty-eight patients (47%) reported a ≥50% reduction in seizure frequency. A ≥50% reduction in seizure frequency was reported by 65% and 40% of patients in the nocturnal seizure and diurnal seizure subgroups, respectively ($p > 0.05$). Of the 28 responders, 2 achieved stable periods of seizure freedom of 6 and 11 months after starting LCM. Twenty patients (33%) reported drug-related adverse events (AEs); the most common was dizziness (16 patients). LCM was withdrawn in 8 patients (13%). There were no serious AEs. These results support the efficacy and safety of adjunctive LCM in patients with partial-onset seizures.

1. Introduction

Epilepsy is one of the most common chronic neurological conditions, affecting 0.5–1% of the population worldwide.[1] The goal of antiepileptic therapy is to achieve long-term seizure freedom with minimal adverse events (AEs). Despite advances in epilepsy treatment and the development of new antiepileptic drugs (AEDs), 30% of patients continue to experience uncontrolled seizures.[2,3] Partial epilepsy represents 60% of the drug-resistant epilepsies.[4]

Partial seizures can occur during both sleep (nocturnal seizures) and wakefulness (diurnal seizures); the distribution is variable and differs according to the type of epilepsy.[5,6] Nocturnal seizures profoundly disrupt sleep structure, which can cause daytime somnolence and loss of concentration during daily activities.[5] Also, the risk of sudden unexplained death in epilepsy is increased in patients with nocturnal seizures.[7,8] Therefore, effective treatment of patients with nocturnal seizures is very important. Some studies have shown that AEDs that block voltage-gated sodium channels are more effective than other AEDs for the treatment of nocturnal seizures.[9,10] These findings, as well as evidence that mutations in the voltage-gated sodium channel genes SCN1A, SCN2A, and SCN1B are involved in several types of epilepsy, strongly support the development of additional AEDs acting on voltage-gated sodium channels.[11,12]

Lacosamide (LCM) is a new AED approved as adjunctive therapy for partial-onset seizures. It has a novel dual mechanism of action consisting of selective enhancement of slow inactivation of voltage-dependent sodium channels[13] and modulation of collapsin-response mediator protein 2.[14] Its approval was based on efficacy and safety results from three phase III double-blind placebo-controlled trials,[15–17] but little is known about its efficacy in daily clinical practice,[18] especially in patients with nocturnal seizures.

This study retrospectively analyzed postmarketing data from LCM-treated patients in four Spanish hospitals to characterize the efficacy and safety profile of LCM, and compare its effect in patients with nocturnal versus diurnal seizures.

2. Methods

This observational, retrospective, multicenter study included 60 patients treated with LCM as adjunctive therapy for partial-onset

* Corresponding author at: Epilepsy Unit, Department of Neurology, Hospital Clínico San Carlos, Profesor Martín Lagos, S/N, 28040 Madrid, Spain.
Tel.: +34 913 305 250/630 779 461; fax: +34 915 430 884.
E-mail addresses: ingmorales@hotmail.com, garciamorales2@gmail.com (I. García-Morales).

1059-1311/$ – see front matter © 2011 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.seizure.2011.08.005

seizures. The study was conducted between January 2009 and January 2011 at four epilepsy units in Spain.

All patients received oral LCM tablets as adjunctive therapy for refractory focal epilepsy. None of the patients included in the study had participated in premarketing clinical trials of LCM. The decision to initiate LCM treatment was made according to clinical criteria. To improve the tolerability of LCM, treatment was titrated more slowly than recommended by the manufacturer. Treatment was initiated at 50 mg once daily, followed by weekly increments of 50 mg/day to a target dose of 200–500 mg/day. Doses were adjusted individually depending on seizure control and adverse events (AEs).

All patients gave their written informed consent to the collection of their clinical data for the study. Data were obtained at the sites and later stored in a common database for analysis. Information was recorded on demographics, epilepsy history (duration, seizure type, and etiology), occurrence of nocturnal and diurnal seizures, psychiatric comorbidities, previous and concomitant AEDs, LCM daily dose, seizure frequency (recorded from patients' diaries that were reviewed at each visit to the site), and drug-related AEs. Drug-related AEs were evaluated from spontaneous patient reports and direct questioning at the site.

Epilepsy was classified according to the International League Against Epilepsy criteria.[19] Diagnosis of epilepsy was established by seizure description, age of onset, family history of epilepsy, response to AED therapy, electroencephalography (EEG), and magnetic resonance imaging findings.

Two groups were analyzed: the diurnal seizure (DS) group included patients with >50% of seizures occurring while awake, and the nocturnal seizure (NS) group included patients with >50% seizures occurring during night or daytime sleep. Included patients all slept with someone who was able to recognize seizures to facilitate accurate recording of the number of seizures a patient had. The 50% response rate (proportion of patients with a ≥50% reduction in seizure frequency) was assessed in the overall patient population, and in both the DS and NS subgroups.

3. Results

3.1. Patient characteristics

A total of 60 patients (54% women) were included. The mean age at the time of inclusion was 38.3 years (range 21–69). The average time since diagnosis of epilepsy was 27.2 years (range 1–67). All patients had refractory focal epilepsy with monthly seizures. Patients experienced a mean of 9.7 seizures per month (range 2–60). Seventeen of 60 patients (28%) had >50% nocturnal seizures and were included in the NS group; of these 17 patients, 11 had exclusively nocturnal seizures. The etiology of epilepsy was undetermined in 43% of patients, while hippocampal sclerosis and cortical dysplasia were the most common causes of epilepsy in patients with known etiology (Table 1). Based on the symptomatology of seizures and MRI findings in the cases who had structural alterations on MRI, twenty-two patients (37%) were diagnosed with temporal lobe epilepsy (9 with hippocampal sclerosis) and the remaining patients were diagnosed with extratemporal lobe epilepsy. None of the patients had undergone surgery and therefore the exact epileptogenic area could not be confirmed in the absence of video EEG monitoring.

During the study, patients were taking a mean of 2.2 drugs (range 1–4) and six patients (10%) were taking concomitant antidepressant treatment. The most common background AEDs were levetiracetam (LEV) [25 patients], carbamazepine (CBZ) [19 patients], lamotrigine (LTG) [16 patients], topiramate (TPM) [13 patients], and oxcarbazepine (OXC) [13 patients]. Patients had failed a mean of 6.3 AEDs (range 3–13) before starting treatment with LCM. Patients were followed up on LCM treatment for 13–24 months.

Table 1
Etiology of epilepsy.

Etiology	Number of patients (%)
Hippocampal sclerosis	9 (15)
Cortical dysplasia	8 (13)
Meningoencephalitis	5 (8)
Brain tumor	5 (8)
Perinatal infarct	2 (3)
Brain malformation	1 (2)
Cerebral hypoxia	1 (2)
Ischemia	1 (2)
Mitochondrial disease	1 (2)
Down's syndrome	1 (2)
Unknown	26 (43)

3.2. Efficacy

The stable dose of LCM achieved was 200 mg/day in 31 patients (52%), 300 mg/day in 16 patients (27%), 400 mg/day in 10 patients (17%), and 500 mg/day in 3 patients (5%).

A ≥50% reduction in seizure frequency was achieved in 28 patients (47%), of whom 11, 11 and 6, respectively, were receiving LCM 200 mg/day, 300 mg/day and 400 mg/day. A ≥50% reduction in seizure frequency was observed 11/17 patients (65%) in the NS group and 17/43 patients (40%) in the DS group. The difference between the groups was not statistically significant ($p > 0.05$). In addition, 2 of the 28 responder patients achieved stable periods of seizure freedom of 6 and 11 months after starting LCM. Background AED treatment consisted of valproate and LEV in one of the seizure-free patients, and zonisamide (ZNS) in the other; one seizure-free patient was in the NS group. The percentage of responders in the subgroup of patients who were taking classic sodium channel modulators was 45% (18/40) compared with 75% (15/20) in the subgroup who were not taking this type of AED. Therefore, these data do not indicate that use of LCM with other sodium channel modulators is more effective. However, these data do suggest that the combination of LCM with drugs with a different action mechanism might be more beneficial. Seven patients (12%) reported 30–50% reductions in seizure frequency, of whom 3 were in the NS group, and 17 patients (28%) experienced no change in seizure frequency.

3.3. Adverse events

Twenty out of 60 patients (33%) reported drug-related AEs during LCM therapy (Table 2). The most common drug-related AE was dizziness, which occurred in 16 patients. More than 50% of patients who reported dizziness (12/16) were taking other sodium channel modulators, 7 were taking CBZ and 5 were taking OXC. Doses of CBZ and OXC were reduced, but in 5 cases (42%) LCM had to be withdrawn due to intolerance. Two patients experienced an increase in seizure frequency after they were on LCM. Background AED therapy in these 2 patients consisted of ZNS and OXC in 1 patient, and ZNS and LTG in the other. Both patients improved after LCM was withdrawn. One patient experienced confusion and

Table 2
Drug-related adverse events reported by patients during lacosamide therapy.

Event	Number of patients (%)
Dizziness	16 (27)
Diplopia	4 (7)
Somnolence	2 (3)
Behavioral alteration and agitation	1 (2)
Pain in finger and toe-nails	1 (2)