Lacosamide for refractory generalized tonic–clonic seizures of non-focal origin in clinical practice: A clinical and VEEG study

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Abstract

From September 2009 to March 2016 we identified 9 patients from Hospital Ruber Internacional and San Carlos diagnosed with GGE presenting with persistent GTCS. Diagnosis and terminology utilized were based on the International League Against Epilepsy 1981 and 1989 proposals [13] and 2010 report [14]. Persistence was defined as occurrence of any GTCS at the time of evaluation despite having tried two or more first-line anti-seizure drug (ASD) for GGE. Other causes of treatment failure were excluded: alcohol/drug abuse, poor compliance, extreme lack of sleep and non-epileptic events. Informed oral consent for the off-label treatment with LCM was obtained. LCM was started as adjunctive therapy. Collection of data of the 9 patients was retrospective. The ethics committee of Hospital Clinico San Carlos approved this study. The primary efficacy endpoint was responder rate: percentage of patients achieving ≥50% reduction in GTCS frequency during the 6 months after LCM initiation compared to the 6 months before. We reviewed the total period of follow-up of patients to exclude posterior aggravations, measure the duration of seizure freedom, register other side effects and changes on ASD regimen.

To reinforce the identification of any aggravation of absences or myoclonia, a 24-hour VEEG was performed on all patients during the first case series, video-EEG (VEEG) was performed during follow-up.

2. Material and methods

We identified 9 patients with GGE and persistent GTCS. Demographic and clinical data are illustrated in Tables 1 & 2.
3.1. Results on GTCS

In addition to GTCS, two of the 9 patients had refractory absences, and one had absences, myoclonia and GTCS in the 6 months before LCM treatment onset.

Eight patients were currently or had been on valproate (VPA). Only one female (1, Table 2) was not treated with VPA to avoid adverse effects. LCM was prescribed at a median daily dose of 300 mg (200–400). Patients received an initial dose of 50 mg twice a day in the first week, which was increased in 50 or 100 mg increments per week depending on response and tolerance. In one patient (3, Table 2) titration of LCM was made at the same time progressive tapering of topiramate was performed. In the remaining 8, no change of other ASDs was made during the titration or maintenance on LCM.

3.2. Effect on absences and myoclonia

Among the three patients with absences in the 6 months before LCM, two of them were responders (1, Table 2). After a median follow-up of 155 weeks (interquartile range of [95–170]), 8 of 9 patients remain on LCM. There were no seizure aggravation after the first 6 months. Patients did not report other side effects.

3.3. Follow-up

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3.4. VEEG findings

A 24 hour VEEG on LCM therapy was performed in 8 patients. It was normal in 2 patients (1&4, Table 2), whose previous EEG had shown generalized spike-and-wave discharges. Two more patients had moderately persistent generalized epileptiform discharges only during sleep (3&5, Table 2). They had not undergone prolonged VEEG before LCM.

Table 1
Demographic and clinical characteristics.

| Sex | Age, years: mean (SD) | Age at onset, years: mean (SD) | Number of prior ASDs: median (IQR) | ASDs combined to LCM (n) | VPA dose, mg: median (IQR) | Number of GTCS/6 months pre-LCM: median (IQR) |
|-----|----------------------|-------------------------------|-----------------------------------|--------------------------|---------------------------|----------------------------------|
|     | 46.9 (10.3)          | 13.2 (6.3)                    | 3 (3–5)                           | VPA (6), LEV (4), LTG (1) | 1250 (1050–1450)           | 2 (2–3)                          |

* Excluding patients not taking VPA.

### Table 2
Individual description of cases.

| Patient/sex | Age/age at onset (years) | GGE syndrome | Persistent seizuresa | Seizure frequency before LCMa | ASD regime (mg/24 h) | Clinical responseb | Details |
|------------|-------------------------|--------------|----------------------|------------------------------|----------------------|-------------------|---------|
| 1/F        | 43/20                   | JME          | GTCS                 | 1/6 m                        | LCM 200             | Yes               | 2 y SzF on LCM up to date |
| 2/M        | 39/6                    | CAE persisting into adulthood | ABS and GTCS | 2 GTCS/6 m | Weekly ABS | LCM 300 | Yes | After 3.5 y SzF on LCM, he suffered 2 GTCS (one provoked) in the last year |
| 3/F        | 53/5                    | CAE persisting into adulthood | GTCS | 3/6 m | | LCM 400 | Yes | 6 y SzF on LCM up to date |
| 4/M        | 48/14                   | GTCS alone   | GTCS                 | 2/6 m                        | LCM 200             | Yes               | ABS status on CBZ in the past 5 y SzF on LCM up to date |
| 5/F        | 50/12                   | GTCS alone   | GTCS                 | 3/6 m                        | LCM 200             | Yes               | 3.5 y SzF on LCM up to date |
| 6/M        | 63/10                   | JME          | ABS, myoclonic and GTCS | GTCS/6 m | | LCM 300 | Yes | 3 y SzF on LCM up to date |
| 7/F        | 33/24                   | JAE          | ABS and GTCS | 2 GTCS/6 m | | LCM 400 | Yes | Subjective ABS increase 1.5 y GTCs-SzF on LCM up to date |
| 8/M        | 35/17                   | GTCS alone   | GTCS                 | 2/6 m                        | LCM 400             | No                | Similar, SzF after adding VPA to LCM (attributed to VPA) |
| 9/M        | 58/11                   | JAE          | GTCS                 | 2/6 m                        | LCM 150             | No                | Myoclonic and absence status |

GTCS generalized tonic–clonic seizure; ABS absences; NQ not able to quantify; y years; m months; SzF seizure free; LEV levetiracetam; VPA valproate; LTG lamotrigine.

* In the 6 months prior to LCM treatment onset.

b 50% or greater reduction in GTCS frequency.
to compare. In two other cases (2&6, Table 2) VEEG showed low persistent generalized spike-and-wave discharges. Comparisons to prolonged VEEG before LCM demonstrated reduction of persistence and duration of discharges on LCM in both cases, and disappearance of hyperventilation-induced absences in one of them. In all these 6 cases VEEG findings were in line with their clinical responder rate.

The remaining clinical responder (7, Table 2) had low persistent epileptiform discharges during sleep similar to prolonged VEEG before, in spite of the increase on absence frequency reported. However, VEEG was performed more than a week after clinical aggravation. No seizures were detected.

VEEG in non-responder case 8 showed moderately persistent epileptiform discharges during awakening and sleep. No previous prolonged VEEG was available for comparisons. The only patient who did not have VEEG on LCM suffered status epilepticus (9, Table 2). VEEG had been postponed because of personal issues, as he did not feel any worsening impairment.

4. Discussion

In this case series of 9 patients with GGE in a regular clinical-setting, LCM has been an effective option for the treatment of drug-resistant GTCS. The high responder rate (7/9) should be interpreted in context of difficult-to-treat patients and the long periods of seizure freedom achieved.

In this series, two cases of absence aggravation, one of whom had status epilepticus, were noted, in line with recent clinical evidence supporting the risk of worsening this type of seizure [12]. Wechsler et al. [12] reported a lower absence aggravation rate: 10% of 49 patients plus a unconfirmed episode of absence status.

Regarding myoclonia, the status suffered by a patient without previous history of myoclonia suggests that it could be possible to trigger de novo seizures of this type. As far as we know, this is the first myoclonia and absence status reported with LCM. Recently, another case of unmasking of myoclonia in a patient with GGE on LCM was reported [15] (not a status). In our study, the combination of LCM and lamotrigine could have also facilitated the aggravation. No cases of de novo myoclonia and one transient aggravation were reported by Wechsler [12]. More clinical data are needed to quantify the risk of myoclonia aggravation with LCM.

VEEG findings were parallel to clinical evolution in most cases. By contrast, in patient 7, who experienced a transient aggravation of absences, neither seizures nor increase on epileptiform discharges was detected on 24 hour VEEG. This was probably due to the delay between the clinical worsening and the VEEG, which outlines the importance of VEEG availability for urgent and long-term recordings.

These data, along with the poor correlation between 24-hour ambulatory EEG findings and the clinical changes in absences reported by Wechsler et al., suggest that performing longer EEG and VEEG recordings can improve sensitivity in detecting seizure aggravation.

Our study adds to previous literature a report of a case of status involving myoclonia and absences. New data regarding efficacy of 24 hour VEEG to detect seizure aggravation, as well as further evidence supporting efficacy of LCM in patients with GTCS in GGE. On the other hand, our series has the limitations of a small sample size, the retrospective character of data collection for baseline seizure frequency, and the inclusion of a small number of cases with absences and myoclonia that could be prone to aggravation.

5. Conclusions

In agreement with previous clinical evidence, our results suggest that LCM can be a reasonable option for patients with GGE and persistent GTCS. During follow-up evaluation, prolonged VEEG should be considered to in addition to clinical surveillance, especially in patients with a history of absences who could have a higher risk of worsening. Unmasking of myoclonia, even in the form of status, is also a potential risk, whose quantification from the effect of LCS needs further clinical research.

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