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Case Report

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

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1. Introduction

Genetic Generalized Epilepsy (GGE) accounts for 15–20% of cases of adult epilepsy [1]. Most patients are rendered seizure-free with first-line antiseizure drugs (ASD), which are effective in generalized tonic–clonic seizures (GTCS), absence and myoclonic seizures. Approximately 15% of patients are refractory to these ASD [2]. In this subgroup, GTCS are the most incapacitating seizures, and other ASD are required. Classic ASD that exert their action through fast blocking of the sodium channel can be effective on GTCS, but they have the potential to aggravate absences and myoclonia [3]. Status epilepticus involving absences and myoclonia have been described with carbamazepine, oxcarbazepine and phenytoin [3,4]. Lamotrigine is one of the drugs of choice in GGE, but also has a potential for aggravating myoclonia that is lower than the other classic sodium channel blockers [5–6].

Unlike older sodium channel blockers, that facilitate the fast inactivation of sodium channel, lacosamide (LCM) facilitates the slow inactivation of this channel [7]. First developed for focal epilepsies, LCM was successful in controlling GTCS in GGE in some case series [8–11] and in a recently published safety open label study [12]. However, in this study, 10% of patients suffered an aggravation of absences. Thus, further investigation on its efficacy/aggravation profile over different types of seizures in GGE is highly valuable.

The aim of our observational study was to assess if LCM was effective for GTCS in a series of patients with GGE and control for aggravation or appearance of absences/myoclonia. For this purpose, and in contrast to first case series, video-EEG (VEEG) was performed during follow-up.

2. Material and methods

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 6–12 weeks after LCM initiation. Additionally, we explored the subjective impression of patients by asking if absences or myoclonia had been aggravated.

3. Results

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

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Table 1
Demographic and clinical characteristics.

Sex, females: n, %	4, 44.4%
Age, years: mean (SD)	46.9 (10.3)
Age at onset, years: mean (SD)	13.2 (6.3)
Number of prior ASDs: median (IQR)	3 (3–5)
ASDs combined to LCM (n)	VPA (6), LEV (4), LTG (1)
VPA dose, mg: median (IQR)[a]	1250 (1050–1450)
Number of GTCS/6 months pre-LCM: median (IQR)	2 (2–3)

[a] Excluding patients not taking VPA.

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.

3.1. Results on GTCS

Seven out of 9 patients were responders (1–7, Table 2). Seizure-free periods achieved on LCM were longer than one year in all of them. In two cases they were longer than 5 years.

One of the two non-responders (8, Table 2) did not improve during the first 6 months on LCM, but became seizure-free after adding VPA, remaining seizure free on this therapy after a follow-up of 2.5 years. The remaining patient (9, Table 2) discontinued LCM at the 4th month because of a myoclonia and absence status (described below).

3.2. Effect on absences and myoclonia

Among the three patients with absences in the 6-months before the initiation of LCM, two denied an aggravation in these seizures. The remaining patient (case 7, Table 2) reported a worsening of absences both in frequency and duration around the 4th–7th weeks. Some of these well-described episodes reached 10–15 min, one of them ending with a GTCS. A 24-hour VEEG was performed on the 9th week. Neither seizures, nor aggravation of epileptiform activity was detected. This patient preferred to maintain LCM because she reached good control of GTCS (only one after LCM initiation). Absence frequency was tolerable and remained stable, and the duration of absences improved.

Apart from those three cases, two patients had experienced absences in the past (not in the 6 months before LCM onset). One is case 9, a 58-year-old male with juvenile absence epilepsy. His absences were controlled and he was started on LCM 150 mg/24 hours added to lamotrigine 400 mg/24 hours for persistent GTCS. He remained seizure-free until month 4, when he suffered status epilepticus. The semiology was described by a witness as ongoing absences with involved of the arm during myoclonia that evolved after half an hour to a GTCS with postictal agitation. LCM was withdrawn. He denied previous history of myoclonia. The other one is patient 4, who had a past history of absence status on carbamazepine. He was started on LCM for very persistent GTCS. He did not suffer any aggravation and remains seizure free after 5 years.

The only patient who suffered myoclonia in the 6 months prior to LCM (6, Table 2) reported a significant reduction. There was a second patient with juvenile myoclonic epilepsy (JME) who had suffered myoclonia in the past (1, Table 2). He did not report reappearance.

3.3. Follow-up

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.

3.4. 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 2
Individual description of cases.

Patient/sex	Age/age at onset (years)	GGE syndrome	Persistent seizures[a]	Seizure frequency before LCM[a]	ASD regime (mg/24 h)	Clinical response[b]	Details
1/F	43/20	JME	GTCS	1/6 m	LCM 200 LEV 1000	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 VPA 1200 LEV 1000	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 LEV 3000 VPA 1000	Yes	6 y SzF on LCM up to date
4/M	48/14	GTCS alone	GTCS	2/6 m	LCM 200 VPA 1000	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 LEV 2000	Yes	3,5 y SzF on LCM up to date
6/M	63/10	JME	ABS, myoclonic and GTCS	6 GTCS/6 m NQ for myoclonic and ABS	LCM 300 VPA 1300	Yes	3 y SzF on LCM up to date
7/F	33/24	JAE	ABS and GTCS	2 GTCS/6 m NQ for ABS ("sporadic")	LCM 400 VPA 1600	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 VPA1500	No	Similar. SzF after adding VPA to LCM (attributed to VPA)
9/M	58/11	JAE	GTCS	2/6 m	LCM 150 LTG 400	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.
[a] 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.

References

[1] Jallon P, Latour P. Epidemiology of idiopathic generalized epilepsies. Epilepsia 2005; 46:10–4.
[2] Faught E. Treatment of refractory primary generalized epilepsy. Rev Neurol Dis 2004;1(Suppl. 1):S34–43.
[3] Chaves J, Sander JW. Seizure aggravation in idiopathic generalized epilepsies. Epilepsia 2005;46(Suppl. 9):133–9.
[4] Thomas P, Valton L, Genton P. Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy. Brain 2006;129:1281–92.
[5] Andrade Machado R, Frades García V, Goicoechea Astencio A, Benjumea Cuartas V. Efficacy and tolerability of lamotrigine in Juvenile Myoclonic Epilepsy in adults: a prospective, unblinded randomized controlled trial. Seizure 2013;22:846–55.
[6] Crespel A, Genton P, Berramdane M, Coubes P, Monicard C, Baldy-Moulinier M, et al. Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. Neurology 2005;65:762–4.
[7] Rogawski MA, Tofighy A, White HS, Matagne A, Wolff C. Current understanding of the mechanism of action of the antiepileptic drug lacosamide. Epilepsy Res 2015; 110:189–205.
[8] Afra P, Adamolekun B. Lacosamide treatment of juvenile myoclonic epilepsy. Seizure – Eur J Epilepsy 2012;21:202–4.
[9] Afra P, Strom L, Bainbridge J, Buchanan T, Berry A, Spitz M. Role of lacosamide as adjunctive treatment of adults with primary generalized epilepsy. Abs. 2.159. American Epilepsy Society Conference; 2010.
[10] Arnold S, Beige A. Adjunctive treatment with lacosamide: an option for generalized epilepsy? Abs. 2.209. American Epilepsy Society Conference; 2010.
[11] Zangaladze A, Skidmore C. Lacosamide use in refractory idiopathic primary generalized epilepsy. Epilepsy Behav 2012;23:79–80.
[12] Wechsler RT, Yates SL, Messenheimer J, Leroy R, Beller C, Doty P. Lacosamide for uncontrolled primary generalized tonic–clonic seizures: an open-label pilot study with 59-week extension. Epilepsy Res 2017;130:13–20.
[13] International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1981;22:489–501.
[14] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51:676–85.
[15] Birnbaum D, Koubeissi M. Unmasking of myoclonus by lacosamide in generalized epilepsy. Epilepsy & behavior case reports; 2016. http://dx.doi.org/10.1016/j.ebcr.2016.09.006.