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Case Report

Lacosamide may improve cognition in patients with focal epilepsy: EpiTrack to compare cognitive side effects of lacosamide and carbamazepine

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ABSTRACT

Carbamazepine (CBZ) is a first generation anti-seizure drug, considered as first choice therapy in focal epilepsy but associated with cognitive side effects. Lacosamide (LCM) is a third-generation anti-seizure drug approved for treating focal epilepsy. This case series documented the comparable efficacy of LCM and CBZ as first add on treatments in patients affected by uncontrolled focal seizures. LCM showed an increase in EpiTrack scores, which measure cognitive abilities, at follow-up compared to CBZ. This preliminary data may represent the basis for future prospective studies aimed at comparing the long-term cognitive side effects of LCM and CBZ.

1. Introduction

Lacosamide (LCM) is a widely used third-generation anti-seizure drug (ASD) approved for treating focal epilepsy. LCM treatment has been associated with low risk of cognitive deterioration in patients affected by drug-resistant epilepsy [1]. Moreover, a recent randomized-controlled trial performed in healthy individuals documented that LCM had fewer neuropsychological side effects compared to carbamazepine (CBZ). Therefore, LCM seems to exhibit a favorable cognitive profile in healthy subjects [2]. A previous open-label prospective clinical study investigated the cognitive effects of LCM in drug-resistant epilepsy [3]. It was documented that LCM showed no negative effects on cognition. However, studies investigating the effects of LCM compared to other sodium channel blockers are not present in literature.

EpiTrack represents a valid 15-minute screening tool for detecting and tracking cognitive side effects of ASDs. Moreover, it can monitor the cognitive adverse effects of seizures in patients with epilepsy [4]. It evaluates executive functions, which are altered frequently in patients with epilepsy. Moreover, it is focused at evaluating executive functions since ASDs mainly affect this cognitive domain [5,6].

Therefore, the aim of this case series study was to compare the effects of LCM and CBZ, used as first adjunctive treatment, on cognitive functions measured by EpiTrack in a small population of patients affected by epilepsy.

2. Methods

The present report is a case series including consecutive patients affected by focal epilepsy who started LCM or CBZ as first adjunctive theraphy for their uncontrolled focal seizures from October 2016 to August 2017. Patients were classified according to the 1981 International League Against Epilepsy, which was in use when patients were diagnosed [7]. Since it is common clinical practice at our Epilepsy Centre to fix visits before starting a new therapy and after 3 months of treatment, we collected and analyzed data considering those time points [8–10]. The following data were analyzed: age, gender, time since epilepsy onset, etiology (symptomatic or cryptogenic epilepsy), 1-month total seizure count at baseline and at 3 months after starting LCM or CBZ (follow-up), AEDs history, EpiTrack scores at baseline and follow-up. Titration was performed according to clinical practice for LCM or CBZ. For the statistical analysis we considered: i) 75% responder rate, defined as the percentage of patients obtaining a minimum of ≥75% seizure reduction in seizure frequency compared to baseline, ii) seizure freedom (considered as absence of seizures between time points), iii) EpiTrack scores difference between baseline and follow-up.

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Table 1
Demographic and clinical data of LCM and CBZ patients.

	LCM (n = 8) mean ± SD	CBZ (n = 8) mean ± SD	p value
Age	58.52 ± 8.94	57.12 ± 7.54	NS
Age at diagnosis	49.62 ± 14.92	47.12 ± 11.37	NS
Disease duration	9 ± 7.09	10 ± 5.85	NS
Epilepsy type	4 cryptogenic 4 symptomatic (microvascular lesions)	4 cryptogenic 4 symptomatic (microvascular lesions)	NS
First ASD	4 LEV 2 ZNS 2 PB 1 VPA	5 LEV 2 PB 1 VPA	NA
Mean dose at 3-month FU	262.5 ± 91.61	600 ± 151.18	NA

	Baseline	Follow-up	Baseline	Follow-up	
Seizure per month	2.75 ± 1.16	0.37 ± 0.51	2.37 ± 0.74	0.37 ± 0.52	NS
Patients with seizure reduction > 75%	NA	7/8	NA	6/8	NS
Patients seizure free	NA	5/8	NA	5/8	NS

Abbreviations: CBZ, carbamazepine; LCM, lacosamide; SD, standard deviation; LEV, levetiracetam; ZNS, zonisamide; PB, phenobarbital; VPA, valproic acid; FU, follow-up; AED, antiepileptic drug; NS, not significant; NA, not admitted.

The EpiTrack consists of six subtests requiring attention, cognitive tracking, and working memory. The procedure was explicitly developed to enable repeated testing. The overall administration of EpiTrack takes about 12 to 15 min. All test instructions follow the standard instructions of the respective tests, which were:

- an interference test; this test requires inverse reading of three rows of ones and twos (11212 as 22121). Time needed to perform the tasks is the object of the evaluation;
- the popular Trail-making test (TMT, parts A and B) [11]. This test requires cognitive tracking, psychomotor speed, short-term memory, and cognitive flexibility;
- a maze test; patients are asked to track the maze like driving a car, i.e., going back when a dead end is entered. For retesting, a rotated version of this test is available. This test assesses visual anticipation, planning, and psychomotor speed;
- a verbal fluency task; it requires the subject to write down as many words as possible in 60 s that begin with a designated letter (P and L). In the retest version of this subtest, two other letters are used (R and K).
- working memory; it is assessed by use of the digit span backward task [12].

The statistical analysis was performed using commercial software Statistica 10.0 program, Statsoft Inc., Tulsa, OK, USA [9,10]. Descriptive data were expressed as mean and standard deviation for quantitative analyses. For between-group comparisons the Student's *t*-test was used to compare data.

3. Results

Sixteen patients affected by focal epilepsy who started LCM or CBZ as first add-on therapy were included in this case series. LCM was the first adjunctive treatment in 8 patients, whereas CBZ was prescribed as first add-on therapy in another 8 patients. Demographic and clinical data of the patients included in this series are reported in Table 1. The two groups of patients did not significantly differ in terms of demographic data; moreover, groups did not differ for seizures baseline frequency, disease duration, age of epilepsy onset, and previous ASDs (Table 1). Four patients treated with LCM and 4 patients treated with CBZ showed an unremarkable brain MRI and epilepsy was defined as cryptogenic; on the other hand, 4 LCM patients and 4 CBZ patient were affected by symptomatic epilepsy since they showed brain MRI alterations (description of brain MRI is reported in Table 1).

Analyzing data achieved at 3 months, we documented similar efficacy of LCM compared to CBZ, considering seizure freedom (6/8 vs 5/8) or seizure reduction ≥75% (7/8 vs 6/8) (Table 1).

Considering EpiTrack scores, we documented similar scores at baseline in patients who were prescribed LCM or CBZ (23.87 ± 1.64 vs 23.37 ± 1.3, Fig. 1). At 3-month follow-up we documented the significant increase of EpiTrack scores in LCM patients compared to CBZ patients (26.25 ± 1.03 vs 23.87 ± 1.35, $p < 0.05$, Fig. 1).

	Lacosamide (n=8) *mean±SD*		Carbamazepine (n=8) *mean±SD*	
	Baseline	*Follow-up*	*Baseline*	*Follow-up*
Epitrack	23.87±1.64	26.25±1.03*	23.37±1.3	23.87±1.35
* Lacosamide vs Carbamazepine at follow-up, p<0.05				

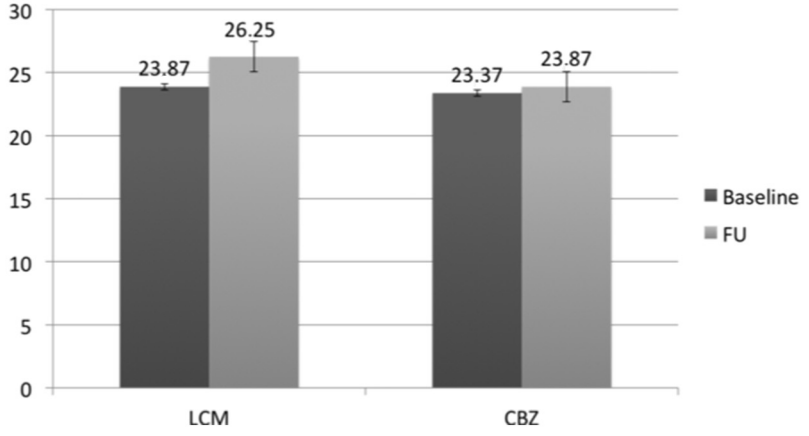

Fig. 1. EpiTrack scores at baseline and 3-month follow-up (FU) in patients treated by lacosamide and carbamazepine.

4. Discussion

This case series documented the positive impact of LCM on Epitrack scores, which reflect cognitive improvement. In particular, Epitrack scores at follow-up were higher in patients who were prescribed LCM compared to those who received CBZ. CBZ is a first-generation ASD acting as sodium channel blocker widely used since its effectiveness in focal epilepsies. CBZ has a specific mechanism of action, which increases its efficacy. However, CBZ shows long-term side effects on cognition. In particular, it has been documented that CBZ may worsen cognitive function and its discontinuation may improve cognition [13]. LCM is a third-generation AED, with a novel mechanism of action promoting the slow inactivation of the sodium channels. It has been demonstrated efficacious in treating focal epilepsy [1]. In this study, we confirmed the similar efficacy of LCM and CBZ. Notably, the novelty of this case series is the possible better cognitive profile of LCM compared to CBZ, as measured by EpiTrack.

Cognition is frequently affected in patients with epilepsy; accordingly, several studies have demonstrated a wider domain of deficits in patients with epilepsy, including executive dysfunction [5,6]. The mechanisms underlying the alteration of cognitive function are not well defined [6]. However, ictal and interictal discharges have been considered the main cause of cognitive deficits in patients with epilepsy [14]. Moreover, neuroimaging studies have also documented functional and morphological brain abnormalities in patients affected by epilepsy, including gray matter atrophy, glucose hypometabolism in several brain areas, and abnormal white matter integrity, suggesting structural causes for cognitive dysfunctions [6,15–17]. Therefore, interventions aimed at preserving or restoring cognition in patients with epilepsy are actually invited, since cognitive impairment appears to be progressive and increases the risk of dementia [18].

EpiTrack is a cognitive assessment already validated to test the cognitive effects of AEDs [19]. Following its validation in healthy subjects, EpiTrack has been tested in patients affected by epilepsy [19]. In particular, it has been used to evaluate the long-term cognitive effects of three ASDs (LCM, topiramate (TPM), and lamotrigine (LTG)). Helmstaedter and co-Authors demonstrated that the cognitive side effect profile of LCM was comparable to that of LTG and superior to that of TPM. In the present case series, we documented the better cognitive profile of LCM compared to CBZ. This data confirmed the beneficial effect of LCM on cognition, and in particular on executive functions. Furthermore, our comparison may be more significant, since CBZ actually represents the best ASD comparator in focal epilepsy, more than LTG or TPM. Notably, we showed the similar efficacy of LCM and CBZ used as first add on treatment in patients affected by focal epilepsy; moreover, patients treated by LCM showed the significant increase of EpiTrack scores compared to patients treated by CBZ. Therefore, LCM may preserve or improve cognition in patients with epilepsy more than CBZ. Our results agree with those of a previous study performed in healthy subjects comparing the cognitive profile of LCM and CBZ. In particular, Authors documented that LCM has fewer untoward neuropsychological effects than CBZ, suggesting that LCM may exhibit a favorable cognitive profile [2]. We confirm this previous data and suppose that LCM may have lesser cognitive adverse effects also in patients affected by focal epilepsy.

We are aware that this case series has several limitations: i) LCM and CBZ efficacy were evaluated in a real life condition; ii) the sample of patients included is small and achieved in a single outpatient epilepsy center; iii) data were not systematically captured but documented in routine clinical records; iv) serum levels of LCM were not captured; v) these results obtained after a short-term follow-up need to be confirmed in studies with a longer follow-up.

5. Conclusions

This clinical investigation comparing the cognitive side effects of LCM and CBZ as first adjunctive therapy in patients affected by uncontrolled focal seizures confirmed the efficacy of LCM and its possible lesser cognitive adverse effect profile. However, since this preliminary observation may represent the basis for future prospective studies aimed at comparing the long-term cognitive side effects of LCM and CBZ, we invite other investigators to participate in further studies in larger populations of patients evaluated at longer follow-up.

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Claudio Liguori, Fabio Placidi, Nicola Biagio Mercuri, Natalia Manfredi and Francesca Izzi declare no conflict of interest or financial disclosures for this study.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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