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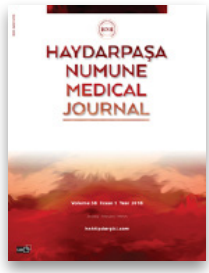

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ORIGINAL ARTICLE

The Efficacy of Lacosamide in Children with Drug-resistant Focal Epilepsy

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Abstract

Introduction: This study aimed to assess the efficacy, tolerability and adverse effects of Lacosamide (LCM) in children with refractory focal epilepsy.

Methods: Children aged younger than 16 years with drug-resistant focal epilepsy were enrolled. The medical records and seizure diaries that were evaluated every three months were reviewed. Response to LCM was defined as ≥50% reduction in seizure frequency.

Results: Twenty-five children with drug-resistant focal epilepsy received LCM as add-on therapy. The mean duration of epilepsy was 5.2 years and the mean age at LCM initiation was 8 years. The rate of response to LCM treatment in the 3th, 6th and 9th months were 44%, 64%, 76%, respectively. At the end of 12 months, the response rate was 84% and 16% of the patients were seizure free. Four patients had adverse effects; three patients were discontinued LCM and one improved after decreasing the dose of the drug.

Discussion and Conclusion: LCM is an effective add-on antiepileptic drug for children with refractory focal epilepsy. It diminishes the frequency of seizures over time. It is well tolerated and a promising option in these patients.

Keywords: Children; drug-resistant epilepsy; focal epilepsy; lacosamide.

Epilepsy is a common and treatable chronic neurological disorder which affects 0.5-1% of all children. Despite the development of new antiepileptic drugs (AEDs) over the past 20 years, up to 30% of patients with epilepsy become refractory to treatment or experience adverse events due to AEDs[1-3]. This situation necessitated the search of new and well-tolerated AEDs and new treatment options to provide an optimal quality of life for the patients.

Lacosamide (LCM) is a third-generation AED, chemically composed of 2-acetamido-N-benzyl-3-methoxypropionamide that selectively enhances slow inactivation component of the neuronal voltage-gated sodium channels. This mechanism diminishes pathological hyperexcitability without affecting physiological activity which is different from other sodium channel blockers[4-6]. It was approved by the Food and Drug Administration as an adjunctive therapy for patients aged 17 years and older with partialonset seizures and in Europe for patients aged 4 years and older with epilepsy[7,8].

In this study, we aimed to present our experience with LCM

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and discuss the efficacy, tolerability and adverse effects of the treatment in children aged less than 16 years with refractory focal epilepsy.

Materials and Methods

Study Design

This retrospective study was conducted between January 2018 and January 2020. The medical records of patients younger than 16 years of age admitted to pediatric neurology department with refractory focal epilepsy and treated with LCM by the same physician (CY) were reviewed. The study was approved by the Ethics Committee of Koc University School of Medicine.

Patients and Assessments

Patients were selected by the following criteria: (1) aged less than 16 years; (2) diagnosed with focal epilepsy; (3) exhibiting at least four seizures per month within the last 3 months in spite of the use of two or more AEDs; (4) have follow-up visits at 3, 6, 9 and 12th months as a minimum.

All patients had biochemical analysis, screening for metabolic disorders, chromosomal investigations, electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) before the treatment and underwent general and neurological examinations every 3 months during LCM therapy. In every follow-up visit, EEG and blood levels of concomitant AEDs were monitored. According to the clinical necessity, peripheral blood count, blood creatinine, urea, alanine and aspartate aminotransferase levels and urinary analysis were done. Additionally, seizure frequency and adverse effect information were recorded by caregivers and reviewed at each follow-up visit.

Collection of Data

Demographics and clinical characteristics including age, gender, aetiology of epilepsy, type and duration of epilepsy, EEG and MRI findings, associated neurological conditions, the number of previous AEDs, the concomitant AED usage, previous treatments such as ketogenic diet, time of response to LCM, final effective LCM dosage, adverse events occuring during the follow-up period and duration of therapy were reviewed.

Lacosamide Treatment

LCM (BENVIDA; Adeka İlac ve Kimyasal Urunler San. ve Tic. A.Ş., Istanbul, Turkey) administered once every 12 hours with a starting dose of 1 mg/kg/d. The dose was increased 1 mg/kg/d every week up to a maximum of 13.6 mg/kg/d.

Response

The seizure diaries were maintained by caregivers. The same pediatric neurologist evaluated the patient's response to the drug and the adverse effects. The decision to continue LCM therapy was made by the pediatric neurologist according to the clinical profile, seizure response and the presence of adverse effects.

The response to LCM was evaluated based on caregiver reports during the follow-up visit and categorized as follows; (1) seizure free; (2) responders who has seizure reduction ≥50%; (3) nonresponders who has seizure reduction <50%; (4) no change in seizure frequency. At each follow-up visit, information regarding adverse events was also noted according to caregiver's report.

Statistical Analysis

The analyses were performed using the SPSS software (Statistical Package for the Social Sciences, Version 21.0, SSPS Inc., Chicago, IL, USA). Continuous variables were expressed as mean±S.D. and categorical variables were expressed as percentages. Differences in continuous variables for 2 groups were analyzed by mann whitney U test. Differences in categorical variables for 2 groups were analyzed by chi square test. Related Samples Mc Nemar test was used to compare ratios of the same group. Statistical significance tested for level of alpha=0.05.

Results

A total of 25 pediatric patients with focal epilepsy treated with LCM were included in the present study. The mean duration of epilepsy was 5.2 years and the mean age at LCM initiation was 8 years. The majority of the population was female (60%). The aetiology was found to be structural in fifteen (60%) patients and unknown in ten (40%) patients. All the patients had abnormal EEG findings and 14 patients (56%) had abnormal MRI findings. Before LCM treatment, the mean number of the AEDs that the patients had been treated with was 3.2. The baseline characteristics of the study population is shown in Table 1.

Before LCM treatment, 2 patients (8%) had tried ketogenic diet and vagal nerve stimulation therapy but it was not found effective in reducing the number of the seizures. The initial dose of LCM treatment was 1 mg/kg/d for all the patients and the mean maintenance dose was 9.7 mg/kg/d (range 5-13.6).

During the study period, 3 patients were excluded in the first three months; two patients had an increase in seizure frequency and one patient had inconsolable crying after

Table 1. Baseline characteristics of the study population

Age, year	8.9
Mean (range)	(2.7-16)
Sex, n (%)	
Male	10 (40)
Female	15 (60)
Duration of epilepsy (year)	5.20
Mean (range)	(0-12.0)
MR Results	
Normal	11 (44)
Anormal	14 (56)
Age at the initiation of the treatment (year)	8.0
Mean (range)	(2-16)
Etiology classification, n (%)	
Structural	15 (60)
Unkown	10 (40)
LCM dose, mg/kg/day	9.74
Mean (range)	(5.0-13.6)
Number of concomitant antiepileptic drug	3.2
Mean (range)	(3.0-5.0)

the initiation of the treatment. Response to LCM treatment is shown in Figure 1. In the 3rd month of the treatment, 44% of the patients were categorized as responder and 56% as non-responder to LCM therapy. In the 6th month of the therapy, the distribution of the population changed to 64% responder and 24% non-responder. The change in the ratio from the 3rd month to the 6th month was not found statistically significant (p=0.063). In the 9th month, the ratio changed to 76% responder and 12% non-responder and the difference was found statistically significant from 3rd month to 9th month (p=0.008). In the 12th month of the treatment, the distribution changed as responder 84% and non-responder 4% and the difference was statistically significant from 3rd month to 12th month (p=0.002).

The responder and non-responder groups were also compared according to gender, age of LCM initiation, duration and frequency of seizures, concomitant AEDs and the mean maintenance dose administered in every 3 months. In the first 3 months of the treatment, the average frequency of seizure was 6.58 in responders and 8.29 in non-responders which was the only variable that was found statistically significant. In the 6th month of the treatment, the variables were not found statistically significant. In the 9th month of the treatment, the average frequency of seziure was 5.45 in responders and 10.0 in non-responders which was found statistically significant (Table 2).

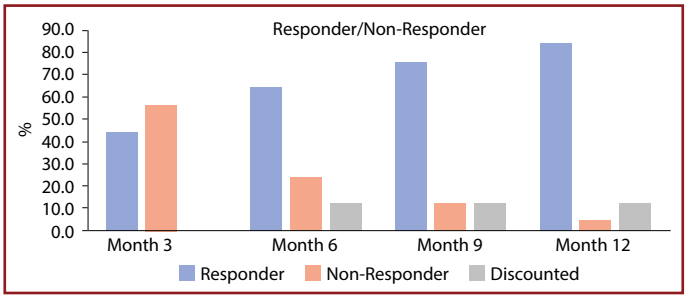

Figure 1. Response to lacosamide treatment.

Discussion

Approximately 30% of pediatric patients with new-onset epilepsy become uncontrolled despite the large number of AEDs on markets[1,9]. Especially during the last two decades, several new generation AEDs have been used for better seizure control with fewer adverse effects and better tolerability. On the other hand, because of ethical causes, the new AEDs were approved just as 'add-on therapies'[1,9-11]. In this retrospective and observational study, the effectiveness and tolerability of LCM as a type of add-on therapy among pediatric patients with refractory epilepsy aged younger than 16 years old are reviewed for 12 months. At the end of 12 months, the retention rate was 88%, the response rate was 84% and 16% of the patients were seizure free.

The adult clinical trials demonstrated that 35-84.9% of older children and adults with refractory seizures who were treated with LCM achieved ≥50% reduction in their baseline seizure frequency[12-14]. Although LCM is used off-label in pediatric population for the treatment of drug-resistant epilepsy, since 2010 several clinical trials are reported focusing on the benefits of LCM treatment in children. The mean response rate which is defined as ≥50% seizure reduction was 30-66%[1,11,13,15]. In the present study, the rate of response to LCM treatment in the 3th, 6th, 9th and 12th months were 44%, 64%, 76% and 84%, respectively. Of 25 patients, 4 (16%) were seizure free similar to the previous studies which was reported as 11-19%[1]. Most studies mentioned that there was no main factor affecting LCM efficacy in the pediatric population. Toupin et al.[16] conducted a study with 22 children with refractory epilepsy and reported that females were more likely to respond to LCM than males. In our study, we did not find gender as an affecting factor for the response to LCM treatment. We also compared responders and non-responders according to frequency of seizure, duration of epilepsy, the concomitant AED usage, age at the start of LCM treatment and final effective LCM dosage and no statistically significant differences were detected between the two groups except the frequency of seizure in the 3th and 9th month of the therapy.

Table 2. Comparison of responder and non-responder groups divided by months

Variables	Responders	Non-responders	p
Month 3			
Gender, n (%)			
Male	4 (36.4)	6 (42.9)	0.534
Female	7 (63.6)	8 (57.1)	
Age in years at start of lacosamide	3.55±1.76	4.00±2.85	0.809
Duration of seziure	5.35±2.88	5.08±3.37	0.687
Frequency of seizure	6.58±2.76	10.00±2.00	0.03
Concominant AEDs	2.45±0.52	2.21±0.43	0.317
LCM dose (mg/kg)	8.99±2.03	10.32±2.16	0.183
Month 6			
Gender, n (%)			
Male	6 (37.5)	3 (50.0)	0.477
Female	10 (62.5)	3 (50.0)	
Age in years at start of lacosamide	3.76±2.23	4.36±2.97	0.802
Duration of seziure	5.35±2.88	4.86±2.90	0.641
Frequency of seizure	6.50±2.94	8.50±2.35	0.059
Concominant AEDs	2.38±0.50	2.33±0.52	0.914
LCM dose (mg/kg)	9.38±2.18	9.74±2.33	0.858
Month 9			
Gender, n (%)			
Male	7 (36.8)	2 (66.7)	0.358
Female	12 (63.2)	1 (33.3)	
Age in years at start of lacosamide	3.79±2.38	4.81±2.78	0.586
Duration of seziure	5.31±3.19	5.11±3.47	0.857
Frequency of seizure	5.45±0.93	8.29±3.07	0.011
Concominant AEDs	2.37±0.50	2.33±0.58	0.929
LCM dose (mg/kg)	9.58±2.29	8.83±1.26	0.651
Month 12			
Gender, n (%)			
Male	8 (38.1)	1 (100.0)	0.409
Female	13 (61.9)	0 (00.0)	
Age in years at start of lacosamide	3.97±2.44	2.92±0.00	0.636
Duration of seziure	5.42±3.15	2.33±0.00	0.364
Frequency of seizure	6.90±2.88	10.00±0.00	0.273
Concominant AEDs	2.38±0.50	2.00±0.00	0.636
LCM dose (mg/kg)	9.50±2.22	9.00±0.00	0.909

In pediatric population there is not a certain mean dose for LCM. Gavatha et al.[17] reported that patients were found to be responder (≥50% in seizure reduction) for a mean period of 8 months at a mean dose of 6.3 mg/kg/d (range 1.710 mg/kg/d). Casas-Fernandez et al.[18] found that higher doses had favorable response on seizure suppression in 16.2% of patients compared to previous studies[17,19]. Rastogi and Ng[20] reviewed 21 pediatric patients with various seizure types who were started on oral LCM as adjunctive therapy for refractory epilepsy. Fifty percent of the patients had greater than 50% reduction in seizure frequency with adjunctive LCM therapy with the final average LCM dose of 9.4 mg/kg/d (range 2.4-19.4 mg/kg/d). Sanmarti-Vilaplana and Diaz-Gomez[21] conducted a study including 191 children with focal epilepsy treated with lacosamide and the dose of LCM, at which response was obtained, was 6 mg/kg/day (range: 1.3-12 mg/kg/d). The rate of reduction in seizure ≥50% was reported in 45% of the patients. Hmaimess et al.[22] conducted a study with 58 patients with a mean age of 10 years experiencing a mean of 36.2 seizures per month with focal-onset seizures. The mean daily LCM maintenance dose was 6.4 mg/kg (range: 2.8–10.0 mg/kg)

and responder rates were ranged between 50% and 68% and seizure free rates ranged between 13% and 38%. In the present study, the average dose of LCM was 9.74 mg/kg/d (range: 5-13.6 mg/kg/d). We observed 84% responder rate and 16% seizure free rate at 12 months following initiation of add-on treatment with LCM.

LCM has oral bioavailability of nearly 100% and has 15% plasma protein binding rate. It is eliminated by metabolic biotransformation and urinary excretion[23]. It has been reported to be a safe and well-tolerated drug. In adult studies, the common adverse effects were reported as dose dependent and those effects were reversible with dose reduction or interruption[24]. Numerous adult and childhood studies demonstrated that the adverse effects mainly involve the gastrointestinal and nervous system. Up to 50% of children on LCM therapy, the main reported side effects were headache, dizziness and nausea. Other side effects were ataxia, fatigue, vertigo, vision abnormalities, nystagmus, coordination and gait problems[6,14,25-28]. LCM was well-tolerated in our study group and the majority of the children did not show any adverse effects due to LCM treatment. A 6 year old girl with cerebral palsy and a 4 year old boy with focal epilepsy with unknown etiology had a significant increase in seizure which led them to discontinue the treatment. In addition to those two patients, a 10 year old girl with cortical atrophy had inconsolable crying with no other apparent reason but LCM treatment, the drug was discontinued and the patient was excluded from the study. Furthermore, we observed a dose-dependent relationship between LCM therapy and the development of hallucination. An eleven years old boy who had epilepsy for nine years had dose dependent visual hallucination and the hallucinations disappeared after reducing the dose of LCM.

This study had some limitations. The main limitation of the study is its retrospective design which is based on clinical records. The other limitation is the small sample size. The last limitation is that plasma drug levels were not determined in our study to maintain the optimal dose of the drug. The main strength of our study is that all the patients were followed-up and treated by the same pediatric neurologist which ensured the same criteria applied to all the patients.

Conclusion

This retrospective study confirmed that LCM appears to be an effective, safe and well tolerated drug in children with uncontrolled drug-resistant focal epilepsy. Furthermore, the decision to discontinue the treatment should not be done in short term use of the drug. The significant response was seen after the 6 months of the treatment course. Further studies are needed to validate the use of LCM as one of the first line drugs and a widely prescribed AED for the treatment of focal epilepsy in childhood.

Ethical Committee Approval: The study was approved by the Ethics Committee of Koc University School of Medicine (2020.320. IRB2.089).

Peer-review: Externally peer-reviewed.

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Conflict of Interest: None declared.

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