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Research Article

Efficacy of Lacosamide Therapy in Focal Onset Refractory Epilepsy of Childhood: A Single Center Experience

Çocukluk Çağının Fokal Başlangıçlı Dirençli Epilepsisinde Lakozamid Tedavisinin Etkinliği: Tek Merkez Deneyimi

Halil Ural Aksoy
Celil Yılmaz
Senem Ayça
Aslı Kübra Atasever
Muzaffer Polat
Sercan Öztürk

ABSTRACT

Objective: *Treatment of childhood refractory epilepsy is a challenge for clinicians. Lacosamide is a new generation antiepileptic drug which is being used for focal onset seizures of adults and children. Efficacy and safety of the drug for adults have been demonstrated in various studies. The aim of this retrospective cross-sectional study is to evaluate the efficacy and safety of lacosamide in childhood refractory focal seizures in our clinic.*
Methods: *We examined the medical records of 14 patients treated with lacosamide in our clinic between January 2016 and January 2020 in terms of demographic, etiological, neuroimaging findings, responses to treatment, adverse effects and drug-drug interactions. We evaluated the patients as responders to treatment whose seizure frequency decreased ≥%50 after 6 months of lacosamide treatment.*
Results: *In 12 patiens (%85.7) seizure frequency decreased ≥%50 (p<0.001) while 5 of them (%35.7) was seizure free. Despite to the long term treatment one patient did not response to lacosamide treatment, and 1 patient's treatment stopped due to aggravation of seizure after initiation of lacosamide treatment. Clinical adverse effects were observed in 3 (%21.4) patients. Cardiac adverse effects or drug-drug interactions were not observed in any patient.*
Conclusion: *As a result of our study, we think that lacosamide is an effective and reliable treatment option for refractory focal seizures of childhood similar to the results of the studies cited in the literature. We also think that further investigations are needed to evaluate its efficacy in focal and different type of seizures of childhood.*

Keywords: *Childhood, focal epilepsy, lacosamide*

ÖZ

Amaç: *Çocukluk çağının refrakter nöbetlerinin tedavisi klinisyenler için zorluk oluşturmaktadır. Lakozamid, yetişkinlerde ve çocuklarda fokal başlangıçlı nöbetler için kullanılan yeni nesil bir antiepileptik ilaçtır. İlacın yetişkinler için etkinliği ve güvenliği çeşitli çalışmalarda gösterilmiştir. Bu retrospektif kesitsel çalışmanın amacı refrakter fokal nöbetleri olan ve lakozamid tedavisi başlanan hastalarda tedavinin etkinliğini ve güvenilirliğini değerlendirmektir.*
Yöntem: *Ocak 2016 ve Ocak 2020 tarihleri arasında kliniğimizde lakozamid tedavisi alan 14 hastanın tıbbi kayıtlarını demografik, etiyolojik, görüntüleme bulguları, tedaviye yanıtları, tedavi yan etkileri ve ilaç-ilaç etkileşimleri açısından inceledik. Tedavinin 6. ayında nöbet sıklığında ≥%50 azalma olan hastaları tedaviye yanıtlı olarak değerlendirdik.*
Bulgular: *On iki hastada (%85,7) nöbet sıklığında ≥%50 azalma izlenirken (p<0,001) bunlardan 5 tanesinde (%35,7) tam nöbet kontrolü sağlandı. Bir hastada uzun dönem lakozamid kullanımına rağmen tedaviye yanıt alınamadı, bir hastamızda ise tedavi sonrası nöbet sıklığında artış olması nedeni ile ilaç kesildi. Toplam 3 hastamızda (%21,4) klinik yan etki izlendi. Hiçbir hastamızda kardiak yan etki veya ilaç-ilaç etkileşimi izlenmedi.*
Sonuç: *Çalışmamızın sonucunda lakozamid tedavisinin etkinliği literatürdekine benzer şekilde yüksek olarak izlendi. Lakozamidin çocukluk çağı refrakter fokal nöbetlerinde etkili ve güvenilir bir tedavi seçeneği olduğunu düşünüyoruz. Çocukluk çağının fokal nöbetlerinde ve diğer nöbet tiplerinde etkinliğini ve güvenilirliğini değerlendirmek için daha fazla araştırmaya ihtiyaç olduğunu düşünüyoruz..*

Anahtar kelimeler: *Çocukluk çağı, fokal epilepsi, lakozamid*

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Halil Ural Aksoy
Celal Bayar Üniversitesi Tıp Fakültesi,
Çocuk Nöroloji Bilim Dalı,
Manisa, Türkiye
uralaksoy@hotmail.com
ORCID: 0000-0003-3131-1808

C. Yılmaz 0000-0002-0951-8258
S. Ayça 0000-0001-7486-9655
A.K. Atasever 0000-0003-2608-0443
M. Polat 0000-0002-1291-6417
Celal Bayar Üniversitesi Tıp Fakültesi,
Çocuk Nöroloji Bilim Dalı,
Manisa, Türkiye

S. Öztürk 0000-0002-7952-5656
Celal Bayar Üniversitesi Tıp Fakültesi,
Çocuk Sağlığı ve Hastalıkları
Ana Bilim Dalı,
Manisa, Türkiye

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INTRODUCTION

Epilepsy is the most common chronic neurological disease in childhood. With a properly selected monotherapy, seizures can be controlled in approximately 2/3 of patients, while approximately 30% of patients have refractory seizures despite proper use of multiple antiepileptic drugs [1]. Since most antiepileptics used in the treatment of refractory epilepsy have similar mechanisms of action, decreased activity or increased toxic effects of antiepileptics as a result drug-drug interactions in polytherapy are common problems. Non-pharmacologic treatments such as epilepsy surgery, vagal nerve stimulation (VNS) and ketogenic diet have limited indications, in addition to difficulty of administration and variable treatment response rates among patients. Because of these treatment difficulties in patients that have refractory epilepsy, several studies on the development of new antiepileptic drugs evaluation of their post-marketing effectiveness and safety are ongoing [2].

Lacosamide (LCM) is a new-generation antiepileptic drug that reduces neuronal membrane excitability with slow inactivation of sodium channel [3]. LCM also modulates collapsin response mediator protein (CRMP-2), which is an intracellular messenger effective in neuronal growth, axonal sprouting and myelinization [4]. However, the clinical effect of this mechanism is not fully understood. Thanks to its mechanism of action different from other sodium channel blockers, lack of its induction or inhibition by hepatic enzymes, low rate of binding to serum proteins, high renal clearance rates, and linear pharmacokinetics, LCM has low drug-drug interaction and advers effect profile [5]. LCM was first approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of focal seizures in adult patients. In our country, it was approved for use in resistant focal seizures in adults in 2012, and pediatric patients with refractory focal seizures over 4 years old in 2016 [6].

In this retrospective cross-sectional study, we evaluated efficacy and the safety of LCM in children with refractory focal seizures.

MATERIAL and METHODS

The records of patients who were treated with LCM and followed-up at our clinic between January 2016 and January 2020 were retrospectively examined. Patients with ≥50% reduction in their seizure frequencies after 6th month of treatment were accepted as responders to treatment. Patients were evaluated as for age, gender, seizure etiology, and semiology; Electroencephalography (EEG), Magnetic Resonance Imaging (MRI) Electrocardiography (ECG) findings; types, numbers and serum levels of antiepileptic drugs used concomitantly or before LCM treatment; non-drug antiepileptic therapies such as VNS, ketogenic diet, and epilepsy surgery. After obtaining these information, all patiens evaluated in our clinic in terms of seizure frequency, adverse effects of the treatment, serum drug levels, control EEG and ECG findings.

Statistical analysis was performed by using IBM SPSS 20 package program. Descriptive statistics were expressed as percentages, mean ± standard deviation, or median (minimum-maximum) according to the normality distribution. McNemar chi-square test was applied for categorical variables. Type 1 error value was evaluated as 5%, and a p-value of <0.05 was considered statistically significant. Ethical approval for our research was obtained from local ethics committee (2020/66).

RESULTS

Patients' Demographic Data: Fourteen children (female n=3 21.4%, male n=11 78.6%, and mean age: 8.64 years) on LCM add-on therapy included in the study (Table 1). Cranial MRI was normal in 3 patients (21.4%), while 11 patients (78.6%) had various pathological findings in their cranial MRI. The average number of antiepileptic drugs used by patients after being diagnosed with epilepsy was 3.29 (range: 2-6). All patients used at least two antiepileptic drugs (max: 4, mean: 2.4) at the beginning of treatment. The most commonly used antiepileptics in decreasing order of frequency were levetiracetam (n=13),

Table 1. Demographic, clinic informations and treatment responses of patients

Patient	Male	Age (year)	Etiology	Concomitant AED	Duration of Treatment (Month)	≥%50 Seizure Reduction	Seizure Free	Adverse Effects
1	M	13	İdiopathic	LEV, VPA, CLB	16	Yes	Yes	None
2	M	16	HİE	LEV, VPA	26	Yes	Yes	Aggression, behavior change
3	M	9	Choroid plexus papilloma	VPA, CBZ	25	Yes	Yes	None
4	M	12	Epileptic encephalopathy	LEV, VPA	1	No	No	Seizure aggravation
5	M	16	İdiopathic	LEV, VPA	34	Yes	Yes	Nausea and vomiting
6	M	10	HİE	LEV, TPR, OXC	14	Yes	No	None
7	F	16	Neurodegenerative disease	LEV, VPA, TPR	14	Yes	No	None
8	M	7	Trauma/ICB	LEV, VPA	16	Yes	Yes	None
9	F	13	HİE	LEV, CBZ	13	Yes	No	None
10	M	9	Meningitis sequelae	LEV, VPA, CBZ, TPR	12	No	No	None
11	M	14	HİE	LEV, VPA	11	Yes	No	None
12	F	13	Structural/CCA	LEV, VPA	15	Yes	No	None
13	M	12	Structural/Cerebellar athropy	LEV, VPA	12	Yes	No	None
14	M	8	Trauma/ICB	LEV, VPA	8	Yes	No	None

AED:Antiepileptic drug, HİE Hypoxic ischemic encephalopathy, İCB:Intracranial bleeding, CCA: Corpus callosum agenesis, LEV:Levetiracetam, VPA:Valproic acid, CLB:Clobazam, CBZ:Carbamazepine, OXC:Oxcarbazepine:, TPR:Topiramate.

sodium valproate (n=12), carbamazepine (n=3), topiramate (n=3), oxcarbazepine (n=1), and clobazam (n=1) respectively. Our four patients (28.6%) were using sodium channel blocking antiepileptics along with LCM. None of the patients had received non-drug antiepileptic treatments. When the laboratory values were examined in the 6th month of the treatment, liver and kidney function tests of all our patients were found to be normal. Serum concentrations of valproic acid, carbamazepine and phenobarbital were examined in the 6th month of the treatment. Serum drug concentrations of all of our patients who used these antiepileptics were within normal range. Serum levels of other antiepileptics could not be tested in our clinic.

Etiology: Etiological examination revealed that 2 patients (14,3%) were classified as idiopathic epilepsy, while 12 patients (85,7%) had symptomatic epilepsy. The most common etiology was hypoxic-ischemic encephalopathy (HIE) (n=4, 28.6%), trauma-related bleeding and brain damage (n=2, 14.3%), congenital structural anomalies of brain (n=2, 14.%), choroid plexus papilloma (n=1), meningitis sequelae (n=1), neurodegenerative disease (n=1) and epileptic encephalopathy (n=1) respectively.

Seziure semiology: All of fourteen patients had the same seizure semiology (focal-onset seizures). Isolated focal seizures were observed in 6 patients (42.9%), while 8 patients (57.1%) had secondary generalized seizures with focal onset. The mean age at the onset of seizures was 35.5 months (range: 1 month-10 years).

EEG findings: Several epileptiform anomalies were present in all patients' EEGs before initiation of the treatment. Focal epileptiform anomalies were observed in 8 patients (57.1%), while 6 patients (42.6%) had generalized epileptiform anomalies. Eleven (78.6%) patients had moderate-to-severe mental-motor developmental delay.

Efficacy: The mean age of initiating LCM treatment was 12 years (median: 12-13). LCM has given in an average dose of 9.57 mg/kg/day (lowest: 8, highest: 12 mg/kg/day) after three weeks titration period. The mean duration of treatment for all our patients was 15.5 months (range: 1-34 Months). When ignoring the patient whose treatment was terminated in the 1th month due to aggravation of the seizure. the average duration of treatment was 16.62 months (Range: 8-34 Months).

In the 6th month of the treatment, in 12 patients (85,7%) seizure frequency decreased by ≥50% compared with the beginning of the treatment ($p<0.001$). Five patients (35.7%) were seizure-free. LCM treatment was discontinued at the 1th month

after the number and frequency of seizures increased in the patient with the diagnosis of electrical status epilepticus of slow sleep (ESES). The patient is still being followed-up with a diagnosis of epileptic encephalopathy. In one patient, despite using lacosamide for 12 months, there was no significant decrease in the frequency of seizures. When the total number of seizures of our patients was evaluated, the average number of seizures before treatment was 18,86/month while it was found to be 7.14/month in the first year of treatment (p<0.001) (Table 2).

When we examined the effect of LCM therapy by gender and etiology, the p-value could not be calculated because the data did not meet the statistical assumptions due to the low number of units in females (3/11), and patients with idiopathic epilepsy etiology (2/11). Clinical Treatment-related clinical adverse effects were observed in 3 patients (21.4%) The symptoms of a patient with complaints of nausea and vomiting, and another patient with complaints of hyperactivity and aggressiveness were disappeared after dose regulation and did not require drug discontinuation. However, there was a significant increase in the number and frequency of seizures after treatment in the patient we followed with the diagnosis of ESES. The treatment of this patient was discontinued in the 1th month. Subsequently the patient diagnosed as epileptic encephalopathy with unknown etiology. No abnormalities were found in the QT/QTC or PR intervals in the follow-up. No major change was observed in EEG of any patient in the 6th month of their treatment.

Table 2. Seizure frequencies at the first year of treatment.

	Before LCM treatment mean±sd (25P-75P)	At the first year of LCM treatment mean±sd (25P-75P)	p
Average seizure frequency (number of seizures per month)	18.86±30.69 (4.00-15.00)	7.14±17.11 (0.00-1.75)	<0.001

LCM: Lacosamide, sd: Standard deviation.

DISCUSSION and CONCLUSION

LCM therapy in refractory childhood focal epilepsies was approved, and several researches regarding efficacy and safety of the drug is ongoing. Recently, in a broad review including 26 studies and 797 patients (refractory epilepsy and epileptic syndromes n=757, status epilepticus n=40) demonstrated that 50.07% of the cases had a decreased frequency of seizures at a rate of ≥50%, and 23.62% of the patients were seizure-free during an average follow-up period of 10.23 months after LCM treatment. The drug efficacy rates among the studies included in the review were quite different (0%-100%) [7]. The reason for these different treatment response rates seem to be due to the highly heterogeneous age ranges, seizure types, seizure etiologies, drug dose, and duration of drug use of the patients in the studies. But in studies performed with only groups of patients with focal-onset seizures, the efficacy of LCM was found to be higher [8-10].

The first randomized, double-blind, placebo-controlled study for efficacy and safety of LCM in childhood focal seizures was published in 2019. The study included 306 patients (LCM=152, placebo=154, mean age=10.7), and ≥50% decrease in seizure frequency on the 28th day of treatment was found to be statistically significant (p=0.0006) in the LCM group, compared to the placebo group [11]. LCM treatment seems to be more effective in focal-onset seizures of childhood in literature. In our study, efficacy of LCM in focal-onset seizures was quite high (85,7%), like those cited in the literature. However, the number of patients in our study was small. The age range, gender (female/male: 3/11) and etiologies (idiopatic/symptomatic: 2/12) of our patients were comparable to each other. We think that high response rates to LCM treatment in our research are likely due to these factors.

Studies on the efficacy of LCM in special epileptic syndromes of childhood are limited. In a study of 18 patients with Lennox-Gastaut syndrome -a specific epileptic encephalopathy, efficacy of LCM treatment was low (33%) with a higher seizure aggravation rate (17%) [12]. In our study, seizure aggravation was observed in one male patient with a diagnosis of

ESES, who was diagnosed as epileptic encephalopathy in his follow-up. The average follow-up period of our cases was more than 1 year (mean=15.5 months) in line with the literature. In some studies seizure control rates at the end of the first year of treatment was significantly lower than the seizure control on the 28th day [8,13]. In our study, seizure frequency of the patients significantly decreased ($p<0.0001$) at first year of treatment compared to their seizure frequency before treatment (Table 2).

There is no common consensus on the dose of lacosamide in childhood, however, the recommended dose is 8-12 mg/kg/day [14]. In the literature, various dose ranges (2.4-19.4 mg/kg/day) were used, but any difference in dose-related efficacy was not reported [7]. In our study, the drug was used according to the dose range recommended by the manufacturer (mean=9.57mg/kg/day). In our patients no relationship was found between dose and clinical response.

The most common adverse effects during treatment are dizziness and somnolence, similar to those in adult patients. Headaches, tremors, ataxia, behavioral disorders and aggression have been also observed. These adverse effects are usually seen in the titration phase of the drug and can be controlled by dose adjustments. Most commonly adverse effect which requires discontinuation of treatment is the aggravation of seizures [3,7,11,14,15]. The mechanism of seizure aggravation is unknown. Although it is stated that the frequency of adverse effects increases with concomittant use of a classical sodium channel blocker, there are no findings to support this suggestion [16]. LCM treatment apparently has a favourable safety profile as for cardiac system and no arrhythmias or QT/QTc and PR interval changes have been detected during treatment in childhood patients [3,17]. No pathological ECG findings were found in any of our patients who used drugs for more than 6 months. The adverse effects such as dizziness and somnolence, which are the most common adverse effects seen in the literature, were not observed in our study. Behavioral change and aggression observed in one of our patients, and nausea-vomiting symptoms in one patient were controlled by dose titration. Initially we could not understand whether the increase in seizures in our patient with epileptic encephalopathy was due to medication or the course of the disease. Since seizures decreased after drug withdrawal, we thought that this was an adverse effect of the drug. Serum levels of sodium valproate, carbamazepine, and phenobarbital were within normal ranges in patients receiving these treatments. In our clinic serum levels of other drugs could not be analyzed. Most of our cases (78.6%) were unable to state their subjective complaints due to having moderate-severe mental and motor developmental delays. Parents and caregivers might not remember the symptoms at the beginning of treatment. We think that these two factors are mainly causes of low adverse effect rate (21.4%) detected in our study distinctively different from literature data.

In our country, permission from the national drug agency is required for LCM treatment in patients younger than 16 years old. Therefore, the number of patients in our study was small. Another limitation in our study was the inability to compare statistical assumptions because gender (female/male=3/11) and etiological (idiopathic/symptomatic=2/11) distributions were not close to each other.

In conclusion, results of our study and other studies in the literature suggest that LCM is an alternative treatment with high efficacy and safety in the treatment of focal-onset refractory seizures in childhood. We think that more prospective randomized, placebo-controlled studies with a wider number of patients are needed to evaluate its efficacy and safety in focal and other type of seizures and epileptic syndromes of childhood.

Ethics Committee Approval: Manisa Celal Bayar University Faculty of Medicine Clinical Research Ethics Committee approval was obtained (27.01.2020/66).
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