The Role of Add-On Lacosamide Therapy in the Treatment of Focal Onset Epilepsy

Focal Başlangıcılı Epilepside Lakozamidin Ek Tedavideki Yeri

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Summary

Objectives: The aim of this study was to retrospectively evaluate the efficacy and safety of lacosamide (200-300-400 mg/day) as adjunct treatment in patients with uncontrolled focal-onset seizures taking 2 or more antiepileptic drugs (AED).

Methods: The medical records of patients with uncontrolled focal epilepsy who received lacosamide as add-on therapy for at least 6 months was reviewed retrospectively. The demographic data, the doses of lacosamide, concomitant AED therapy, and seizure activity in first and sixth months were analysed.

Results: A total of 83 patients were evaluated. The mean percent reduction in seizure frequency per month was 38.98% in the first month and 33.22% in the sixth month. In all, 53% of the patients had a decrease in seizures of 50% or more in the first month, and 47% saw a similar decrease in the sixth month. The percentage of those taking a sodium channel blocking AED in addition to lacosamide was 97.6%. Dose-related adverse events reported included dizziness, nausea, diplopia, gastroenterological side effects, headache, itchy skin, and blurred vision. It was determined that all of the patients with drug-related side effects were taking a sodium channel blocking AED concomitantly with lacosamide.

Conclusion: Adjuvant treatment with lacosamide reduced seizure frequency for patients with uncontrolled focal-onset seizures.

Keywords: Efficiency; focal epilepsy; lacosamide.

Özet

Amaç: İki veya daha fazla antiepileptik ilaç (AEİ) kullanan ve nöbetleri durmayan fokal başlangıçlı epilepsi hastalarında lakozamidin 200–300–400 mg/gün dozunda ek tedavi olarak kullanılmasının etkinliği ve güvenilirliğini geriye dönük olarak incelenmesi amaçlandı.

Gereç ve Yöntem: Nöbetleri durmayan ve ek tedavi olarak en az altı ay boyunca lakozamid kullanlan fokal başlangıçlı nöbetleri olan hastaların tıbbi kayıtları geriye dönük olarak incelendi. Demografik veriler, lakozamid dozu, birlikte kullanıldığı AEİ tedavisi ve birinci ve altını aylardaki nöbet aktivitesi incelendi.

Bulgular: Toplam 83 hasta değerlendirildi. Nöbet şıklığındaki ortalama azalma birinci ayda %38,88, altını ayda %33,22 ve tedaviye %50 yanıt oranı birinci ayda %53, altını ayda %47 olarak bulundu. Lakozamid ile birlikte kullanılan ve sodyum kanalı üzerinden etkili AEl oran %97,6 olarak bulundu. Doza bağlı olarak etkiler sersemlik, bulantu, diplopi, gastrointestinal yan etkiler, baş ağrısı, kaşıntı ve görme bulanıklığı olarak bulundu. Ilaç yan etkisi tespit edilen hastaların hepsinin lakozamid ile birlikte sodyum kanalı üzerinden etkili eden AEİ kullandığı tespit edildi.

Sonuç: Kontrol altına alınmayan fokal başlangıçlı nöbetleri olan hastalarda ek laksazamid tedavisi nöbet şıklığını azaltmaktadır.

Anahtar sözcükler: Etkinlik; fokal epilepsi; lakozamid.
Introduction

Epilepsy is one of the most common neurological diseases affecting up to 2% of the world’s population. It is characterized by at least two unprovoked seizures due to the excessive electrical activity of the brain and periodic alterations in neurological functions effective on consciousness. Epileptic seizures can be divided as generalized and focal-onset seizures. Focal epileptic seizures start in a localized area of a hemisphere of the brain, however, the seizure activity may sometimes spread to the whole brain, which is known as secondarily generalized seizure.

The half of the patients can be seizure free on the first antiepileptic drug (AED) and approximately 60-70% can be controlled on monotherapy, usually with the the first or second AED chosen. Therefore, the treatment of epilepsy usually involves the use of multiple AED, and the patients need to comply and adopt the long-term treatment. Despite of the new AEDs in recent years and proper care, about 30% of patients continue to experience seizures and are exposed to side effects. Giving additional AED treatment to drug resistant patients is accepted as a standard method. Although monotherapy, polytherapy, epilepsy surgery and neurostimulation are still used, there is a continuing need for the development of new AEDs with high tolerability, which reduces the frequency and severity of the seizure and can be used safely.

Lacosamide (LCM) consists of newly developed functionalized amino acids (R-2-acetamido-N-benzyl-3-methoxypropinamide). It seems to have a dual mode of action. It provides the stabilization of hyperexcitable neuronal membranes by selectively enhancing slow inactivation of voltage-dependent sodium channels, and inhibits repetitive neuronal firing without affecting physiological neuronal excitability. In Turkey, it has a license to be used as an additional treatment for focal-onset epilepsy patients since October 2012.

In this study, we aimed to investigate treatment efficacy, tolerability, and side effects of LCM as an additional treatment in patients with focal-onset epilepsy and with ongoing seizures, despite the use of at least two AEDs.

Materials and Methods

This study is a multi-center retrospective study. The data of 4397 patients, who were followed with the diagnosis of epilepsy, were reviewed retrospectively. Data of patients with focal-onset epilepsy, who were at the age of 16 or above, who met the criteria for LCM add-on-therapy due to uncontrolled seizures despite of using two AEDs for at least six months, and who started LCM treatment, were obtained. Monthly seizure frequency of the patients before LCM treatment and on the first and sixth months follow-up of the treatment was evaluated. Demographic characteristics of patients, whether the seizures were generalized, the number of different AED molecules they used throughout their lives, the number of AED they used with LCM, LCM dose, and side effect profile were obtained from the medical records of the patients. Patients, who discontinued the medication due to side effects or intolerance in less than six months, were recorded separately. Decrease in the seizure frequency was evaluated according to the percentage data. Reduction in seizure frequency by 50% or more was considered as that the treatment was beneficial for the patient. This retrospective study was approved by the local ethics committee.

Statistical analysis

The study data were analyzed using SPSS version 16.0 software package (Statistical Package for the Social Sciences Inc; Chicago, IL, USA). The variables were tested for conformity to normal distribution using visual (histogram) and analytic methods (Kolmogorov-Smirnov). Descriptive data were expressed as mean and standard deviation for normally distributed variables or median and minimum-maximum values were used for non-normally distributed variables. Normally distributed variables were compared with Student’s t-test in independent groups whereas dependent groups were compared using t test. Non-normally distributed variables or non-continuous variables were compared with Mann-Whitney U test in independent groups and with Wilcoxon test in dependent groups. Differences in frequency were compared with Chi-square test in independent groups and with the McNemar test in dependent groups. A p value <0.05 was accepted as statistically significant.

Results

LCM treatment was observed to be started in 97 of the 4397 patients whose medical records were examined. Ten patients were not included in the study since the duration of treatment was less than six months. Two patients were excluded from the study since the medication was stopped in less than six months due to blurred vision in one of them and inability to tolerate gastrointestinal side effects in the
other one. Medications of two patients were found to be stopped in less than six months, as the LCM treatment was ineffective, and those patients were excluded from the study. Data of 83 patients, who met at least six months of treatment, were examined.

Of the patients, 43 were females and 40 were males. Mean age was 32.86±10.50. The mean duration of epilepsy was 16.75±10.45 years. The mean number of seizures per month was found as 14.77±20.99. The median of different AED molecules used lifelong before the LCM trial was found to be 5 (2–9) whereas the median of different AED molecules taken along with LCM was found to be 3 (2–4). Of the patients, 37.3% were using two, 44.6% were using three, and 18.1% were using four concomitant antiepileptic comedication with LCM, and the most commonly used AEDs were levetiracetam (59%), carbamazepine (53%), lamotrigine (39.7%), topiramate (38.5%), valproic acid (34.9%) and zonisamide (28.9%). The ratio of AED affecting over the sodium channel was found to be 97.6%. Demographic characteristics of patients and data on LCM are given in Table 1.

In the review of data on LCM, the range of maximum doses was between 200–400, with median 200 mg/day. LCM re-

<table>
<thead>
<tr>
<th>Table 1. Demographic characteristics of patients and data on LCM use</th>
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<tbody>
<tr>
<td>Total number</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age (Mean±SD)</td>
</tr>
<tr>
<td>Seizure type</td>
</tr>
<tr>
<td>Those with and without secondarily generalized seizure</td>
</tr>
<tr>
<td>Duration of disease (Mean±SD)</td>
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<tr>
<td>Seizure frequency (monthly) (Mean±SD)</td>
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<tr>
<td>Different number of AEDs molecules used lifelong before the LCM (Median, minimum-maximum)</td>
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<tr>
<td>The number of different AEDs molecules used with LCM (Median, minimum-maximum)</td>
</tr>
<tr>
<td>AEDs (%) used with LCM (used by the &gt;20% patient) (%)</td>
</tr>
<tr>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Carbamazepine</td>
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<tr>
<td>Lamotrigine</td>
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<tr>
<td>Topiramate</td>
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<tr>
<td>Valproic acid</td>
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<tr>
<td>Zonisamide</td>
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<tr>
<td>The number of different AEDs (%) used with LCM, which affect through sodium channels</td>
</tr>
<tr>
<td>Duration of LCM use (months) (Mean±SD)</td>
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<tr>
<td>LCM dose (mg/day) (Median, minimum-maximum)</td>
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<tr>
<td>Number of patients in whom side effects were observed (%)</td>
</tr>
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</table>

LCM: Lacosamide; AEDs: Antiepileptic drugs; SD: Standard deviation.

reduced the seizure frequency by more than 50% in 44 patients (53%) in the first month control and in 39 patients (47%) in the sixth month control. The difference was not statistically significant (p<0.05). When a decrease in seizure frequency in the first and sixth months before and after the treatment was examined quantitatively, the reduction rates of seizure frequency were found as 38.98% in the first month and 33.22% in the sixth month. The difference was statistically significant (p<0.05) (Fig. 1). At the end of the first month, seizure freedom was obtained in 12 patients, and this status continued in eight patients at the end of the sixth month. In four patients, the seizures were recurred. The pa-

Fig. 1. Efficacy of the LCM add-on-therapy at the first and sixth months

Fig. 2. Side effects observed in patients due to LCM add-on-therapy.
Patients were receiving LCM treatment for about 12.31±5.43 months. In 25 patients (25.3%), side effects were detected. These side effects were determined as dizziness in six patients, headache in five patients, diplopia in three patients, gastrointestinal side effects in three patients, itching in two cases and blurred vision in two patients (Fig. 2). AEDs of the patients, for whom side effects were detected, were determined as carbamazepine (57.1%), levetiracetam (47.6%), zonisamide (42.8%), topiramate (38%), lamotrigine (38%), valproic acid (33.3%), and all patients were using AED acting through sodium channel. Treatment of two patients was determined to be stopped in less than six months due to gastrointestinal side effects and blurred vision, and those patients were left out of evaluation. According to the histories of the patients, vagal nerve stimulation was applied to five patients, and four patients underwent epilepsy surgery.

In randomized, double-blind placebo controlled studies on LCM, the of decrease in seizure frequency was found as 26–35.3% at 200 mg/day, 36.4–41.1% at 400 mg/day, and 37.8–38.1% at 600 mg/day. Fifty percent and more seizure reduction rates, which were determined as response to treatment, were found as 35–38.1% in the 200 mg/day group, 38.3–49.4% in the 400 mg/day group, and 41.2–49.2% in the 600 mg/day group. The dose of 400 mg LCM per day was found to be more tolerable than the dose of 600 mg.[14–16] In our study, data were retrospective, and the rate of decrease in seizure frequency was 38.98%, and 50% and more seizure reduction rate determined as response to treatment was 53% in the first month evaluation. In the evaluation performed at the sixth month, the rate of decrease in seizure frequency was found as 33.22%, and the rate of clinical response to treatment was 47%. There was no differences in the rates of clinical response to treatment between the first and sixth months. The effectiveness of the difference was not evaluated due to the absence of the placebo group, and our study was found to have similar characteristics with the

**Table 2. Evaluation of groups with and without secondarily generalized seizures**

<table>
<thead>
<tr>
<th></th>
<th>Group with secondarily generalized seizures (n=62)</th>
<th>Group without secondarily generalized seizures (n=21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of the epilepsy (year) (Mean±SD)</td>
<td>16.32±9.71</td>
<td>18.04±12.57</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Seizure frequency (in a month) (Mean±SD)</td>
<td>13.64±9.71</td>
<td>18.04±12.57</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>AEDs number used for lifelong (Median, minimum-maximum)</td>
<td>5 (2–9)</td>
<td>5 (2–8)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>The number of AEDs used with LCM (Median, minimum-maximum)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LCM dose (mg) (Median, minimum-maximum)</td>
<td>200 (200–400)</td>
<td>200 (200–400)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LCM duration (months) (Mean±SD)</td>
<td>12.33±5.79</td>
<td>12.23±4.32</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Decrease rate in seizure frequency (first month)</td>
<td>%38.80</td>
<td>%39.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Decrease rate in seizure frequency (sixth month)</td>
<td>%31.6</td>
<td>%37.6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>50% response rate to the treatment (first month)</td>
<td>%51.6</td>
<td>%57.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>50% response rate to the treatment (sixth month)</td>
<td>%43.5</td>
<td>%57.1</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

LCM: Lacosamide; AEDs: Antiepileptic drugs; SD: Standard deviation.

**Discussion**

In our study, we observed that the efficacy of LCM add-on-therapy in the sixth month was not different from those in the first month, although the rate of reduction in seizure frequency was observed to be decreased. Similarly, seizures were found to be recurrent at the sixth month in four patients who were seizure-free at the first month. The condition, where the patient become seizure-free after the medication, but the seizures recur within the sixth months, is called as honeymoon effect.[13] In our study, it can be said that medication had the honeymoon effect in these four patients.
randomized controlled trials. Short-term benefits of LCM, which has been started to be used on site, was determined to be compatible with the literature. Chung et al.\(^1\) found that the response was higher in the group with secondarily generalized seizure. In our study, there was no difference between the groups with and without secondarily generalized seizures in terms of treatment response. The reason for this may be that Chung et al.\(^1\) calculated the decrease in the number of generalized seizures in their study and a reduction in the total number of seizures in the group, who had secondarily generalized seizure in a period of their lives, was evaluated in our study. In conclusion, the decrease in the number of generalized seizures is significant, and this shows that LCM add-on-therapy not only reduces the number of seizures but also reduces the severity of the seizure.\(^1\)

In an open-ended study on the long-term effects of LCM add-on-therapy, Husain et al.\(^1\) evaluated the treatment efficacy in >1, >2, >3 and >4 years, and the decrease in the seizure frequency was found to be 53.4%, 55.2%, 58.1% and 62.5%, respectively, and the ≥50% response rate was 52.8%, 56.5%, 58.7% and 62.5%, respectively. These ratios show that the efficacy of treatment increased over time, and the medication adherence of patients decreased over time (75%, 63%, 54%, 29%, respectively). The reasons of discontinuing the medication were found as inefficacy by 26%, and side effects by 11%. In our study, the response rate to treatment was not changed and the decrease in seizure frequency was found to be reduced in the sixth month evaluation. The most commonly reported side effects of LCM add-on-therapy occur in the central nervous and gastrointestinal systems and are dose-related.\(^1\) The most common side effects are dizziness, nausea, diplopia, blurred vision, headache, vomiting, ataxia, somnolence, and nystagmus.\(^1\) In a study by Steinhoff et al.,\(^1\) the open-ended data of 511 patients receiving LCM add-on-therapy were evaluated, and the most common side effects were found as dizziness (21.7%), fatigue (15.9), headache (11%), diplopia (10.6), nausea (9.6%), and vertigo (8.8%). Discontinuations because of adverse effects were found as dizziness (5.3%), fatigue (2.5%), diplopia (2.2%), and nausea (2%). In our study, side effects were observed as dizziness (7.2%), headache (6%), diplopia (3.6%), gastrointestinal side effects (3.6%), itching (2.4%) and blurred vision (2.4%), and all patients were using other AEDs with LCM, which are acting through the sodium channel. The side effects that were effective as to cause the treatment to be stopped were blurred vision (1%) and itching (1%). The reasons of less number of side effects in our study may be that the treatment dose was increased more slowly so that patients can tolerate the drug, when needed. In randomized double-blind placebo-controlled trials, the protocol of weekly dose increase by 100 mg/day and dose reduction by 100 mg/day only in cases where the patient feels intolerance, and a strict dose application protocol may cause a decrease in tolerance.\(^1\)

Characteristics of an ideal AED can be specified as having high oral activity and good tolerability, being taken once or twice a day, having minimal drug interaction, and being free of seizure agitation.\(^1\) Clinical trials have shown that LCM can meet these criteria.\(^1\) Response to a new AED is associated with the seizure frequency and number of previously used AEDs.\(^1\) Although the study population where the LCM was used as an add-on-therapy, it was found to be effective when used at 400 and 600 mg/day doses. In our study, the patient profile was a group of patients whose seizures continued despite of two AED treatments for at least six months, and 200 (200–400) mg/day dose median and treatment efficacy were found to be similar with the literature. The first study on LCM was carried out by Genç et al.,\(^2\) and they presented 14 patients in their study. They stated that the individuals included in their study were the patients to whom LCM treatment was started through importing drug from abroad, and LCM was started to be paid back by the social security institution on September 2014, and it could be used more commonly in the following period. In our study, both the patients to whom LCM treatment was started through importing drug from abroad and patients to whom the medication was started after the LCM was started to be paid back by the social security institution were included. To the best of our knowledge, this is the study which was carried out with the widest series in our country, and our findings were found to be compatible with the literature. It was found to be effective, despite of being used in patients with focal epilepsy whose seizures continued despite of at least two AED treatments. Retrospective nature of the study and the absence of a placebo control group are the limitations of our study.

In conclusion, LCM add-on-therapy was found to decrease the frequency of seizures and increase the response rate by 50%. Polypharmacies are required to be determined to better determine the efficacy of LCM in the add-on-therapy for the focal-onset epilepsy, and multi-center and placebo control studies of long-term follow-ups are needed to reduce both the side effects and seizure frequency. In the literature, LCM has been shown to be effective in monotherapy.\(^3\)}
Its license has been taken to be used as monotherapy in our country, however, has not been included in the scope of reimbursement yet. Within this process, we concluded that multi-centered studies with large number of cases and long-term follow-up will better show the place of LCM treatment in our country with its increasing usage both in add-on-therapy and monotherapy.

**Ethics Committee Approval**
Local ethics committee approval was obtained.

**Peer-review**
Externally peer-reviewed.

**Conflict of interest**
The authors declare that they have no conflict of interest.

**Authorship Contributions**

**References**