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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

The Honeymoon Effect in Adult Patients with Refractory Partial-Onset Epilepsy Under Levetiracetam Add-on Treatment

Refrakter Parsiyel Başlangiçli Epilepsili Yetişkin Hastalarda Levetirasetam Ekleme Tedavisinin Balayı Etkisi

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Summary

Objectives: Resistance to antiepileptic drugs has occurres in some patients. The aim of this study was to evaluate the patients with refractory partial epilepsy who initially responded to levetiracetam (LEV) add-on therapy and who had the seizure frequency return to their baseline after a honeymoon period.

Methods: Seven patients with refractory epilepsy, who had transient seizure control with LEV add-on therapy, were included in this study. Age, sex, detailed medical history, epilepsy duration, seizure frequency, concomitant AEDs, time to seizure occurrence after the initiation of LEV, side effects of LEV, cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) data were collected for each patient.

Results: Mean age was 26.14±5.14 years. Three patients were male and the other four were female. Mean seizure frequency before LEV treatment was 8.71±5.25 /month. The seizure-free days with levetiracetam add-on therapy was 51-82 days. After the honeymoon effect, seizure frequency returned to the baseline level and did not changed despite an increase in dosage. Cranial MRI was normal in two patients, while interictal EEG was normal in two patients.

Conclusion: The resistance to LEV add-on treatment in patients with refractory partial onset seizures may develop, but the honeymoon effect of LEV was longer in our patients when compared to the drug's literature.

Key words: Levetiracetam; partial seizures; epilepsy; refractory seizures; drug resistance.

Özet

Amaç: Antiepileptik ilaç tedavisine direnç bazı hastalarda görülebilmektedir. Bu çalışmanın amacı başlangıçta levetirasetam (LEV) ekleme tedavisine yanıt veren ve balayı periyodu sonrası nöbet frekansı başlangıç düzeyine gelen hastaları değerlendirmektedir.

Gereç ve Yöntem: Geçici olarak levetirasetam ekleme tedavisiyle nöbet kontrolü sağlanan refrakter epilepsili yedi hasta çalışmaya alındı. Her bir hasta için yaş, cinsiyet, ayrıntılı tıbbi özgeçmiş, epilepsi süresi, nöbet frekansı, kullanılan antiepileptik ilaçlar, LEV başlandıktan sonra nöbet görülünceye kadar geçen süre, LEV yan etkileri, kraniyal manyetik rezonans görüntüleme (MRG) ve elektroensefalografi (EEG) verileri gözden geçirildi.

Bulgular: Ortalama yaş 26.14±5.14 yıl idi. Üç hasta erkek ve diğerleri kadındı. LEV tedavisi öncesi ortalama nöbet sayısı 8.71±5.25/aydı. Levetirasetam ekleme tedavisi sonrası nöbetsiz gün sayısı 51-82 gündür. Balayı dönemi sonrası nöbet frekansı önceki haline döndü. Bu frekans doz artımına ragmen değişmedi. İnteriktal EEG iki hastada normalken kraniyal MRG iki hastada normal bulundu.

Sonuç: Refrakter parsiyel başlangıçlı nöbetlerde LEV ekleme tedavisine direnç gelişebilir, fakat bizim hastalarımızda LEV balayı etkisi ilaç literatürüyle karşılaştırıldığında daha uzundur.

Anahtar sözcükler: Levetirasetam; parsiyel nöbetler; epilepsi; sık nöbetler; ilaç direnci.

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Introduction

Epilepsy is one of the most common neurological disorders and it affects about 1% of population.[1] This chronic condition is often difficult to treat because 20-30% of the patients have a refractory form.[2] Standard antiepileptic drug (AED) therapy does not provide optimal management for these patients; therefore, new AEDs are needed. Levetiracetam (LEV), one of the recently introduced AEDs, is the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide.[3] LEV appears to have unique mechanism of action[4] that acts by binding to and modulating the synaptic vesicle protein SV2A.[5] It received FDA approval in November 1999 as adjunctive treatment for adults with partial-onset seizures[6] and has been subject to several clinical trials since then.[3,7-9]

LEV is rapidly and almost completely absorbed following oral administration. It exhibits linear pharmacokinetics and the likelihood of accumulation in the body is rare.[10] It is eliminated entirely through renal excretion and, drug interaction potential is absent or negligible[11] because its pharmacokinetics profile includes minimal protein binding and lack of hepatic metabolism (not cytocrome P450 dependent).[12] The LEV tolerability profile regarding the effects on memory and cognitive function are also good.[13] LEV is administered twice daily and can be initiated twice daily, and reaches a steady state after two days.[10]

LEV is efficient in controlling seizures from the first week of drug initiation, during up-titration and throughout the first months of treatment.[14] Some epilepsy patients rapidly develop resistance to AED. LEV resistance was also reported in some cases.[15] In the present study, we have evaluated the patients with refractory partial epilepsy who initially responded to add-on LEV therapy, but after its use had their seizure frequency return to the initial level.

Materials and Methods

Seven patients with refractory epilepsy, who had transient seizure control with LEV add-on therapy, were included in this study. All seven patients initially responded to LEV treatment, but then had their seizure frequency return to baseline after a period of time. They were followed up in the Epilepsy Unit of the Ankara Research and Training Hospital between December 2004 and February 2008. Age, sex, detailed medical history, epilepsy duration, seizure frequency, concomitant AED's, time to seizure occurrence after the initiation of LEV, and side effects of LEV were collected for each patient. Electroencephalography (EEG) and cranial magnetic resonance imaging (MRI) were also investigated. Seizure frequency was determined using a seizure diary completed by each patient or caregiver.

Patients signed an informed consent form before their treatment. LEV was given at a dose of 500 mg twice daily (1000 mg/day) as an add-on therapy. The dosage of LEV was increased gradually to a maximum of 3000 mg/day when the seizures recurred.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS 11.0 for Windows; SPSS, USA). The results of descriptive analysis were expressed mean±SD or number of cases and percentage.

Results

Demographic data, seizure frequency, duration of epilepsy, interictal EEG, ictal EEG and cranial MRI findings are summarized in Table 1. Mean age was 26.14±5.14 (Age range: 20-33). Three (42.9%) of these patients were male and the other four (57.1%) were female. Mean partial seizure frequency before LEV treatment was 8.71±5.25 /month (range: 5-20/month). Average duration of the patients' epilepsy was 13.28±5.34 years. The mean number of concomitant antiepileptic medication except LEV was 2.57±0.53. The most common AEDs used by the patients were sodium valproate and carbamezapine followed by lamotrigine. The mean seizure-free day with LEV add-on therapy was 64.00±10.28 (range 51-82). After this period, the frequency of seizures returned to baseline level. Seizure frequency did not changed, although LEV was increased in two successive doses as 2000 and 3000 mgs/day. One patient had vertigo and dizziness, a side effect attributed to LEV. The treatment was not stopped since those effects were mild and disappeared within one week.

Cranial MRIs revealed changes indicating right hippocampal atrophy in three patients. The remaining four patients had normal cranial MRI. Interictal EEG was normal in two patients. Four patients underwent long term video-EEG monitoring. Ictal activity was determined in two of them. One had seizures originating from right mesial temporal region. She was a surgical candidate. The other patient with ictal EEG findings had bi-temporal epilepsy and she was

Table 1. Demographic data, seizure frequency, duration of epilepsy, interictal EEG, ictal EEG and cranial MRI findings

Age/ Sex	Epilepsy duration (year)	Partial seizure (freq/month)	Other AED (mg/day)	Seizure free day after LEV	Kranial MRI	Interictal EEG	Ictal EEG
20/F	19	8	Sodium valproate 1500 Carbamezapine 1000 Lamotrigine 200	63	R hippocampal atrophy	R temporal sharp waves	R mesial temporal
33/M	9	6	Sodium valproate 1500 Carbamezapine 1200 Lamotrigine 200	71	Normal	Bitemporal sharp waves	–
28/M	11	6	Sodium valproate 1500 Carbamezapine 1200	61	Normal	R>L bilateral centrotemporal sharp waves	–
22/F	19	6	Oxcarbazepine 1800 Sodium valproate 1500	82	Normal	R temparoparietal sharp wave	–
28/F	17	10	Sodium valproate 1500 Carbamezapine 1200	65	R hippocampal atrophy	R>L bilateral temporal sharp waves	Bitemporal
31/M	13	20	Sodium valproate 1500 Carbamezapine 1200 Lamotrigine 200	51	Normal	Normal	No lateralization and localization
21/F	5	5	Carbamezapine 1200 Lamotrigine 400	55	R hippocampal atrophy	Normal	R hemisphere

F: Female; M: Male; R: Right; L: Left.

not suitable for surgery. Origin of the ictal focus could not be determined in the remaining.

Discussion

In this article, we report patients with partial seizures, who responded to LEV add-on treatment initially. AED resistance developed 51-82 days later. A similar return to the baseline seizure frequency after an initial response to an add-on AED during the first month of treatment was reported by Boggs et al.[16] for several AEDs including carbamazepine, phenytoin, lamotrigine and gabapentine. Resistance to LEV treatment was also reported previously.[15,17,18] Glien et al.[17] have tested LEV in a rat model of temporal lobe epilepsy with spontaneous recurrent seizures. They separately investigated the effect of LEV for the first and second week of treatment and found that the significant anticonvulsant effect determined in the first week was partially diminished in the second week. They suggested that tolerance might have developed in some rats. Another study in amygdala-kindled rats showed mild reduction in the anticonvulsant effect of LEV after three weeks of treatment.[18]

In the literature, a case with daily seizures and resistance to LEV treatment was reported by Friedman and French.[15] The patient was initially responding to LEV add-on treatment, but this effect was transient and seizure frequency returned to the baseline after one week. They recommended LEV once weekly and found that the patient had significantly fewer seizures on the day of and after administration. They suggested intermittent LEV therapy was a useful treatment strategy for patients with refractory epilepsy who have developed resistance to AEDs .[15]

The mechanism of LEV resistance is not known. According to the literature, the resistance develops quickly.[15,17,18] A previous study showed that LEV acts by binding to and modulating the synaptic vesicle protein SV2A.[5] We do not know how LEV exerts its antiepileptic effects by interacting with this protein. Long-term LEV exposure may alter the chemical structure of protein; this may explain why some patients become resistant to long-term LEV therapy.

In our patients, the resistance to LEV add-on treatment occurred 51-82 days later, a period longer than that reported

in the drug's literature. The honeymoon effect was mainly observed in the first month[16] and LEV resistance appeared in rats after the first[17] and third[18] weeks of treatment. We cannot explain why our patients had a longer honeymoon period. However, hereditary factors may be responsible for this variation. Intermittent LEV therapy was not given to our patients, because our patients could not predict their seizures and/or their seizures' frequencies were not in regular intervals.

In our study, one patient had right temporal lobe epilepsy and another had bilateral temporal lobe epilepsy when we investigated their ictal EEG. The seizure semiology of the remaining two patients, who had ictal EEG, were mainly extra-temporal, although certain localization and/or lateralization could not be made. Three patients did not undergo video-EEG monitoring. However, the seizure semiology and interictal EEG suggested temporal lobe epilepsy.

In conclusion, although LEV provides efficient control as an add-on drug in the treatment of certain intractible partial epileptic seizures early positive response may be reversible in some cases even in maximum therapeutic doses.

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