Is Levetiracetam Monotherapy Effective And Safe In Children With Epilepsy?

Epilepsili Çocuklarda Levetirasetam Monoterapisi Etkili Ve Güvenli midir?

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ABSTRACT

Introduction: Levetiracetam a second-generation antiepileptic drug with a broad spectrum and a wide safety margin, is used in both focal and generalized seizure treatment. In this study, we decided determine efficacy, side effects and safety of levetiracetam monotherapy in children with epilepsy.

Methods: The medical records of consecutive 102 patients who were treated with levetiracetam monotherapy were evaluated retrospectively.

Results: Total of 102 patients on levetiracetam monotherapy, 50 (49%) girls and 52 (51%) boys, were evaluated. Median age of the patients is 121.5 (62.25-178.5) months. Majority of the patients (95.1%) had generalized epilepsy. Twenty-seven (26.5%) patients had concomitant neurological problems. Dosing of levetiracetam was 20-80 mg/kg/day. Twenty eight (27.5%) patients had adverse reactions. The most common side effects were nervousness (10.8%) and enuresis nocturna (3.9%). Nervousness (4.9%), enuresis nocturna (1%) and headache (1%) were the reason for discontinuation. Twenty four (51.1%) of abnormal pre-treatment EEG had recovered and 74 (72.5%) of patients were seizure free after levetiracetam treatment. There was a statistically significant difference between levetiracetam treatment pre- and post-EEG abnormality (p=0.001). All over 10 (9.8%) patients were discontinued the treatment due to adverse effects (n:7, 6.9%) and inefficacy (n:3, 3%) at the 12 month of the treatment. The retention rate was 90.2%.

Conclusion: This study suggests that levetiracetam monotherapy had high percentage of seizure reduction, low rates of serious adverse events and inefficacy, significant difference on pre-treatment EEG recovery in children.

Key words: Adverse reaction, children, efficacy, epilepsy, levetiracetam, monotherapy

ÖZET

Giriş: Geniş spektrumlu ve geniş güvenlik marjına sahip ikinci nesil bir antiepileptik ilaç olan levetirasetam, hem fokal hem de jeneralize nöbet tedavisinde kullanılmaktadır. Bu çalışmada epilepsili çocuklarda levetirasetam monoterapisinin etkinliğini, yan etkilerini ve güvenliğini belirlemeye karar verdik.

Yöntemler: Levetirasetam monoterapisi ile tedavi edilen ardışık 102 hastanın tıbbi kayıtları geriye dönük olarak değerlendirildi.

Bulgular: Levetirasetam monoterapisi alan 50 (%49) kız ve 52 (%51) erkek toplam 102 hasta değerlendirildi. Hastaların ortanca yaşı 121,5 (62,25-178.5) aydır. Hastaların çoğunluğu (%95.1) jeneralize epilepsi hastasıydı. Yirmi yedi (%26,5) hastada eşlik eden nörolojik problemler vardı. Levetirasetam dozu 20-80 mg/kg/gün idi. Yirmi sekiz (%27.5) hastada yan etkiler görüldü. En sık görülen yan etkiler sinirlilik (%10.8) ve enürezis nokturna (%3.9) idi. Sinirlilik (%4.9), enürezis nokturna (%1) ve baş ağrısı (%1) bırakma nedeniydi. Tedavi öncesi anormal EEG'nin 24'ü (%51.1) düzeldi ve levetirasetam tedavisi sonrası hastaların 74'ü (%72.5) nöbetsiz kaldı. Levetirasetam tedavisi öncesi ve sonrası EEG anormalliği arasında istatistiksel olarak anlamlı fark vardı (p=0,001). 10'dan fazla (%9.8) hastanın tamamı, tedavinin 12. ayında yan etkiler (n:7, %6.9) ve etkisizlik (n:3, %3) nedeniyle tedaviyi bırakmıştır. Elde tutma oranı %90.2 idi.

Sonuç: Bu çalışma, levetirasetam monoterapisinin yüksek oranda nöbet azaltma, düşük ciddi yan etkiler ve etkisizlik oranları, çocuklarda tedavi öncesi EEG iyileşmesi üzerinde anlamlı fark olduğunu göstermektedir.

Anahtar Kelimeler: Advers reaksiyon, çocuklar, etkinlik, epilepsi, levetirasetam, monoterapi

INTRODUCTION

Epilepsy is a common neurological disorder in the pediatric population, affecting up to 1% of children (1). Epilepsy is defined as at least two unprovoked (or reflex) seizures occurring >24 h apart or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures (2). Antiepileptic drugs (AEDs) constitute the majority of epilepsy treatment and aim to treat epilepsy primarily with a single AED. While starting a new AED, the drug should be preferred considering its efficacy, safety,

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tolerability, side effects, accompanying comorbidities, as relevant to the patient's specific circumstances and epilepsy type. With the increasing use of new AEDs in children with each passing day, the issue of which one to choose becomes more and more debatable.

Levetiracetam a second-generation antiepileptic drug with a broad spectrum and a wide safety margin, is used in both focal and generalized seizure treatment (3). And also levetiracetam is the only AED with Class I evidence for myoclonic seizures (4). Levetiracetam works differently from most AED, combining with a protein called synaptic vesicle protein 2A (SV2A) in the brain. But the exact mechanism of action is not fully known (5). The use of levetiracetam, also available intravenous form, is increasing day by day in childhood epilepsy.

There are not many studies of levetiracetam monotherapy in pediatric patients with epilepsy. In this study, we decided determine efficacy, side effects and safety of levetiracetam monotherapy in children with epilepsy.

METHODS

The medical records of consecutive 102 patients who were treated with levetiracetam monotherapy at the pediatric neurology outpatient clinic in 2012-2015 were evaluated retrospectively. Seizures were classified according to commission of international league against epilepsy (ILAE) (6). Seizure type was determined based on the history taken from the parents and the video footage, if any. The patients were clinically evaluated at one month after the drug was started and at three-month intervals thereafter. The responses after using levetiracetam were evaluated under two groups (no seizures (seizure-free if they achieved seizure remission for at least 6 months under levetiracetam monotherapy), seizure recurred within three months). Information of patients' gender, age, mental status, neurological findings, pre-treatment and post-treatment electroencephalography (EEG), magnetic resonance imaging (MRI) findings, regarding etiology, seizure type, seizure frequency, medication dosage, efficacy, adverse events, were obtained retrospectively from the medical records. Patients who did not continue to follow-up were excluded from the study.

Routine EEG was performed with electrodes placed according to the international 10–20 system. EEG was evaluated at pre-treatment and at 6–12 months during the post-treatment period. EEG improvement was defined by a pre-treatment EEG that was abnormal and a follow-up control EEG that was normal (no spikes or abnormalities). Levetiracetam was started with a dose of 15 mg/kg/day, and the dose was increased once a week to 80 mg/kg/day. Serum levetiracetam level could not be measured due to the inability to work in our hospital. The study protocol was approved by the Institutional clinical research ethics committee (2011-KAEK-25 2021/06-14).

Statistical analysis

Statistical analyses were performed using SPSS 15.0 (SPSS for Windows, Version 15.0. Chicago, SPSS Inc.) program. Normally distributed variables were presented as mean (standard deviation), and normally distributed variables were presented as median (minimum-maximum). In the comparison between the independent groups, t-test was used for the parametric data and Mann-Whitney U test was used for the non-parametric data. The difference between the categorical data was evaluated by chi-square and Fisher's exact test. Correlation between variables are evaluated by Spearman correlation coefficient and Kendall's Tau-b correlation coefficient for nonparametric variables and Pearson correlation coefficient for parametric variables. The McNemar test is used to determine the differences on a dichotomous dependent variable between two related groups. For estimating the relationships between a dependent variable and one or

more independent variables (regression analyisis is used. *p*-value <0.05 was considered statistically significant.

RESULTS

Total of 102 patients who received levetiracetam monotherapy were included in this study. Of these, 52 (51%) were male and 50 (49%) were female (male/female ratio 1). Median age of the patients was 121.5 (62.25-178.5) months. The clinical follow-up period ranged from one to 72 (mean±SD 18.06±12.02) months. Ninety-seven (95.1%) patients had generalized seizure and five (4.9%) patients had focal seizure. Cranial MRI was performed in almost all patients (n:95, 92.2%). Sixty-eight (71.5%) patients had normal MRI findings. MRI findings, clinical and demographic characteristics are shown in Table 1. Twenty-seven (26.5%) patients had concomitant neurological problems. Accompanying neurological diseases were mental retardation (n:9, 8.8%), central nervous system infection sequela (n:4, 3.9%), cerebral palsy (n:3, 2.9%), macrocephaly (n:2, 2%), neurodevelopment delay due to prematurity (n:2, 2%) and gait disorder (n:2, 2%). One (1%) patient each had microcephaly, meningomyelocele, Neurofibromatosis type 1, hydrocephaly, and speech disturbance. Five (4.9%) patients had genetic disorders. A total of 51 patients (50%) had idiopathic epilepsy, and 44 (43.1%) patients had symptomatic epilepsy. Epilepsy type could not be evaluated in seven (6.9%) patients who could not undergo MRI.

Dosing of levetiracetam was 20-80 mg/kg/day. Twenty eight (27.5%) patients had adverse reactions. Adverse reactions occurred within a median of one (1-3) months after levetiracetam initiation with the exception of the allergic rash. Allergic reactions occurred within the first 10 days of drug initiation. The most common side effects were nervousness (n:12, 10.8%) and enuresis nocturna (n:4, 3.9%). Nervousness (n:5, 4.9%), enuresis nocturna (n:1, 1%) and headache (n:1, 1%) were the reason for discontinuation of levetiracetam. The discontinuation rate due to adverse effects was 6.9%. The adverse reactions have been presented in Table 1.

Table 1. Clinical and demographic characteristics of the Patients

Clinical and Demographic Characteristic	n	%
Gender		
Female	*50*	*49*
Male	*52*	*51*
Seizure semiology		
Focal Onset	*5*	*4.9*
Generalized Onset	*97*	*95.1*
Type of Epilepsy		
Idiopathic	*51*	*50*
Symptomatic	*44*	*43.1*
Unknown	*7*	*6,9*
MRI Findings (n:95, 92.2 %)		
Normal	*68*	*71.5*
T2 Hyperintensities	*8*	*8.4*
Encephalomalacia	*6*	*6.3*
Corpus callosum agenesis	*4*	***4.2***
Cerebral Atrophy	*3*	*3.2*
Delayed myelination	*2*	*2.1*
Hydrocephalus	*2*	*2.1*
Intracranial hemorrhage	*1*	*1.1*
Dandy Walker Malformation	*1*	*1.1*
Pre-treatment EEG (n:96, 94.1%)		
Normal	*44*	*45.8*
Anormal	*52*	*54.2*
Post-treatment EEG (n:89, 87.3%)		
Normal	*59*	*66.3*
Anormal	*30*	*33.7*
LEV dosage (mg/kg/gün)		
<30	*58*	*56.8*
30-44	*40*	*39.3*
45-80	*4*	*3.9*
Adverse reaction* (n:28, 27.5%)		
Nervousness	*12*	*10.8*
Enuresis Nocturna	*4*	*3,9*
Dermatitis	*2*	*1.9*
Allergic reaction	*2*	*1.9*
Decrease in apettite	*2*	*1.9*
Vertigo	*2*	*1.9*
Swear	*1*	*1*
Increase in apetitte	*1*	*1*
Headache	*1*	*1*
Increase In Apetite	*1*	*1*
Abdomianl Pain	*1*	*1*
Acne	*1*	*1*
Tiredness	*1*	*1*
Fussiness	*1*	*1*
Pressure Feeling	*1*	*1*

Table 2. Adverse effects and clinical features.

	Adverse reaction						*P*
	No		Yes		Total		
	n	%	n	%	n	%	
Gender							
Female	*33*	*32.1*	*17*	*16.7*	*50*	*48.5*	*0.14*
Male	*41*	*40.2*	*11*	*10.8*	*52*	*51.5*	
Pretreatment EEG							
Normal	*29*	*30.2*	*15*	*15.6*	*44*	*45.8*	*0.23*
Anormal	*40*	*41.7*	*12*	*12.5*	*51*	*54.2*	
Post treatment EEG							
Normal	*43*	*48.3*	*16*	*18.8*	*59*	*74.2*	*0.7*
Anormal	*23*	*25.8*	*7*	*7.9*	*30*	*25.8*	
MRI							
Normal	*34*	*36.2*	*15*	*16*	*49*	*52.1*	*0.5*
Anormal	*34*	*36.2*	*11*	*11.7*	*45*	*47.9*	
Response to treatment							
Seizure free	*52*	*51*	*22*	*21.6*	*74*	*72.5*	*0.4*
Seizure recurred	*22*	*21.6*	*6*	*5.9*	*28*	*27.5*	
Mental retardation							*0.2*
No	*69*	*67.6*	*24*	*23.5*	*93*	*91.2*	
Yes	*5*	*4.9*	*4*	*3.9*	*9*	*8.8*	
Neurologic diseaase							
No	*55*	*53.9*	*20*	*19.6*	*75*	*73.5*	*0.76*
Yes	*19*	*18.6*	*8*	*7.8*	*27*	*26.5*	

Allergic reaction (dermatitis) is seen only in two (1.9%) patients. Seventeen (60.7%) patients who had adverse reaction were female. There was not any significant difference between gender and adverse reaction (p=0.14). There was no relationship between drug adverse effects and the presence of MRI findings, neurological disease or mental retardation (p>0.05). Clinical features of the patients with adverse reaction are shown in Table 2.

EEG recording was planned for each patient before and after starting levetiracetam. However, it could not be performed all patients due to patient or family incompatibility. EEG had been performed in 96 (94.1%) patients before treatment and in 89 (81.3%) patients during post-treatment. Eighty four (82.4%) patients had both pre-treatment and post-treatment EEG. Of these 84 patients, 47 (56%) had pre-treatment EEG abnormalities and 28 (33.3%) had post-treatment EEG abnormalities. EEG after levetiracetam treatment was normal in 24 (51.1%) of 47 patients whose pre-treatment EEG was abnormal. An exact McNemar's test determined that there was a statistically significant difference in the proportion of patients between levetiracetam treatment pre- and post-EEG abnormality (p=0.001) (Figure 1). Thirty two (66.7%) of 48 male patients and 20 (41.7%) of 48 female patients had pre-treatment EEG abnormality. There was statistically significant difference between gender and pre-treatment EEG (p=0.017). EEG of 18 (n:28, 64.3%) male patients and 6 (n:18, 33.3%) female patients improved after levetiracetam treatment. The improvement in EEG in male patients after treatment was statistically significantly different from female patients (p=0.028). There was not any significant difference between gender and ILAE seizure type (p=0.67), post-treatment EEG (p=0.33), MRI

abnormality (p=0.9), seizure recurrence (p=0.9). There was not any significant difference between pre-treatment EEG abnormality and ILAE seizure type (p=0.1), seizure recurrence after levetiracetam treatment (p=0.61). There was no significant difference in age between the patients whose EEG improved and did not after treatment (p=0.055).

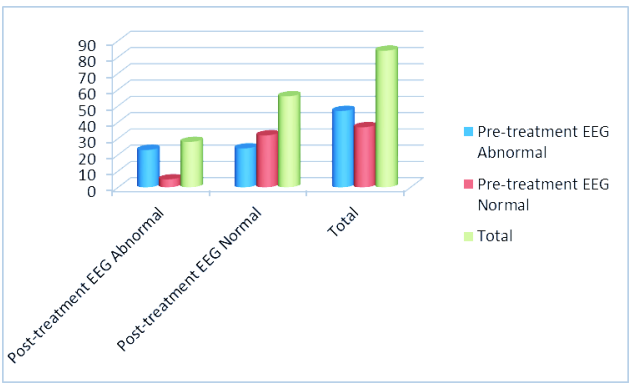

Figure 1. Comparison of EEG before and after levetiracetam treatment.

After levetiracetam treatment, 74 (72.5%) of 102 patients were seizure free. Seventy of seizure-free-patients had pre-treatment EEG. Thirty eight (54.3%) of 70 patients who was seizure free after levetiracetam treatment had abnormal EEG whereas 14 (53.8%) of 26 patients who had recurrent seizures had abnormal EEG before levetiracetam treatment (p=0.9). Fourteen (53.8%) of 26 seizure-recurred-patients had abnormal pre-treatment EEG (p=0.9). Six of (23.1%) of 26 seizure-recurred-patients had abnormal post-treatment EEG (p=0.17). There is not statistically significant difference between post-treatment EEG abnormality and seizure recurrence after levetiracetam treatment (p=0.17).

Levetiracetam treatment was discontinued in seven (6.9%) patients at the third month of treatment. Levetiracetam had been changed another AED in five (5%) patients due to serious nervousness and discontinued in three (2.9%) patients due to inefficacy. Side effects disappeared after levetiracetam was discontinued. All over 10 (9.8%) patients were discontinued the treatment due to adverse effects (n:7, 6.9%) and inefficacy (n:3, 3%) at the 12 month of the treatment. The retention rate was 90.2%. Median duration of levetiracetam treatment was 17 months (8-25.25 months), median seizure free duration was 15 months (9-22 months), seizures recurred in a median of 4.5 months (2-10.5 months). Seizures reccured in 28 (27.5%) patients one of them had focal seizure.

DISCUSSION

Levetiracetam binds to the synaptic vesicle protein SV2A. This may result in neuronal hyperactivation with nonspecific decrease in neurotransmitter release (4). Levetiracetam, as it does not contain enzymes of the cytochrome P450 system, neither induces nor inhibits drugs metabolized by the liver. Since it is largely non-protein bound, it does not compete with other drugs for binding, giving it an advantage in multi-drug use (6,7). In addition, the availability of an intravenous form of levetiracetam increases the frequency of use with each passing day. Although levetiracetam is approved for use as adjunctive therapy in children, it has recently been considered successful as monotherapy (8). Levetiracetam was both effective for partial and generalized seizures (9). Levetiracetam is well-tolerated. It is recommended to adjust the dose by starting at 20 mg/kg/day (infants 1 month to <6 months of age: 14 mg/kg/day) and increasing by 10 mg/kg/day every 1-2 weeks. Target total daily and usual maximum effective dose of levetirecetam by age groups: 4 years to <16 years: 60 mg/kg/day; children 6 months to <4 years: 50 mg/kg/day; infants 1month to <6months: 42 mg/kg/day.4 In this study, majority of the patients (95.1%) had generalized seizures. Levetiracetam was started with a dose of 15 mg/kg/day, and the dose was increased once a week to max. 80 mg/kg/day. Tekgul et al. (10) starting at a dose of 10 mg/kg/day, increased by

10 mg/kg/day at 2-week intervals, maximum dose as needed increased up to 110 mg/kg/day.

As well as the effectiveness, the side effects of the drug are also important for the continuation of the drug. Most common adverse events associated with levetiracetam are asthenia, somnolence and dizziness. Irritability and hostility may occur, more often in children. No relationship was shown between the dosage of levetiracetam and the patient's weight (4,11). In this study, side effects were seen in approximately one-quarter of the patients. The most common side effects were nervousness (10.8%) and enuresis nocturna (3.9%). Side effects were more common in female patients ($p>0.05$). Levetiracetam was discontinued in seven (6.9%) patients due to nervousness, enuresis nocturna and headache. There was no relationship between drug adverse effects and the presence of MRI findings, neurological disease or mental retardation ($p>0.05$). As in this study, nervousness and irritability are the most reported adverse event associated with a high rate of drug discontinuation (12) Headache is one of the frequently reported symptoms in adult patients. Mazur et al. (13) reported side effects in 32.4% patients with irritability, moodiness, depression, and drowsiness being the most common. They had to discontinue levetiracetam in 19.6% of the patients due to the adverse effects. In an another study, it was reported that 16.7% of the patients had side effects in levetiracetam monotherapy (10). The most frequently reported adverse events were irritability, hyperactivity and somnolence. Enuresis was seen in 1.2%. Not only enuresis but also non-seizure-related fecal incontinence has been reported in the literature during levetiracetam treatment (14). Headache, that we had to discontinue levetiracetam treatment in one patient, is one of the common side effects in adult patients (15).

Persistent EEG pathologies were associated with an increased risk for recurrent seizures.16 EEG, which also plays a role in the classification of epilepsy and in the selection of antiepileptic treatment, may play a role in monitoring the effectiveness of AEDs (16,17). Arican et al. (18). evaluated 92 infants with levetiracetam monotherapy, only 32% patients demonstrated improvements on EEG, 83% of them were seizure free. EEG improvement rate was significantly higher in patients who stopped having seizures (12). Tekgül et al. (10) found that levetiracetam effectively improved the EEGs of 47% of the children with focal and generalized epilepsy. In an other study, it was shown the usefulness of levetiracetam in reducing secondary bilateral synchrony on EEG and seizure frequency (19). In this study, EEG had been performed in 84 (82.4%) patients had both pre-treatment and post-treatment EEG. Twenty four (51.1%) of abnormal pre-treatment EEG had recovered after levetiracetam treatment. Levetiracetam treatment was found to be effective in improving EEG ($p=0.001$) There is not statistically significant difference between post-treatment EEG abnormality and seizure recurrence after levetiracetam treatment ($p=0.17$).

Reducing seizure frequency and controlling seizures is one of the most important indicators of the effectiveness of a drug. The retention rate of a drug has been correlated as an indirect indicator of the effectiveness and tolerability of AEDs. And also discontinuation rate was one of the important parameters for the efficacy. In a study investigating the efficacy and safety of levetiracetam monotherapy in children with epilepsy, it was found that 6-month retention rate of 61.1%. Of those patients, 46.8% had seizure free for at least 6 months, 12-month retention rate was 53.1%; also seizure-freedom was 41.2% in 12-months (13). Tekgül and et al. (10) found that the >90% seizure reduction rate of levetiracetam monotherapy in children was 65% in the

3rd month of treatment, and 63% in the 12th month of treatment. In a large cohort of patients with epilepsy, the estimated three-year retention rate of levetiracetam

was 58% (20). In a study comparing the efficacy of levetiracetam monotherapy with carbamazepine and extended-release sodium valproate in newly diagnosed epilepsy patients, it was revealed that levetiracetam did not show significant differences compared to other standard AEDs (21). In this study nearly all patients had generalize epilepsy and 72.5% patients were seizure free after levetiracetam treatment. Levetiracetam was interrupted in only three (2.9%) patients due to ineffectiveness. It was well tolerated with a 12th month discontinuation rate of 9.8%. In this study the retention rate was 90.2%. It was higher than the previous literature.

The main limitation of our study is its retrospective design. We could not compare long-term efficacy, tolerability, and safety of levetiracetam monotherapy to other AED regimen.

CONCLUSION

After levetiracetam treatment, approximately three-quarters of the patients were seizure-free, and levetiracetam was discontinued in only three patients (2.9%) due to ineffectiveness. The retention rate was 90.2%. These results show that levetiracetam monotherapy is well tolerated and effective in children. However, there is a need for multicenter prospective studies with long-term follow-up in children.

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

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