

Efficacy of Levetiracetam Monotherapy in Childhood Epilepsy

Çocukluk Çağı Epilepsilerinde Levetirasetam Monoterapisinin Etkinliği

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Summary

Objectives: Levetiracetam (LEV) is an antiepileptic drug approved particularly for treatment of focal seizures. The aim of this study was to investigate efficacy and tolerability of LEV monotherapy in pediatric patients.

Methods: In the present study, records of 225 children (aged 1 month-18 years) treated with LEV and with follow-up for at least 1 year were evaluated. Diagnosis of epilepsy included history of 2 or more unprovoked seizures. Demographic characteristics, reason for antiepileptic treatment, dosage of levetiracetam, duration of treatment, antiepileptic drugs used previously, seizure type, seizure duration, cranial magnetic resonance images, electroencephalogram results, seizure etiology, and side effects of the drug were documented.

Results: Total of 225 patients, 95 girls and 130 boys, were enrolled in the study. Of those, 125 (55.6%) patients had generalized seizures, 90 (40%) had focal seizures, and 10 (4.4%) had other type of seizures. In treatment, 186 (82.7%) patients remained seizure-free. There was no difference in effectiveness of LEV on partial or generalized epilepsy. Overall, 8 (18%) patients had adverse events. Most common side effects observed were irritability and nervousness. There was no relationship between drug dosage and side effects.

Conclusion: LEV monotherapy is effective in childhood epilepsy with focal or generalized seizures. It is well tolerated in spite of mild and transient side effects, which do not require drug discontinuation.

Keywords: Child; efficacy; epilepsy; levetiracetam; monotherapy; safety.

Özet

Amaç: Levetirasetam çocuk ve erişkinde, özellikle fokal epilepsilerin tedavisinde yaygın olarak kullanılan antiepileptik ilaçlardandır. Bu çalışmada, levetirasetam kullanan çocuk hastalarda ilacın monoterapide etkinlik ve güvenilirliğini belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya, levetirasetam alan ve en az bir yıllık takibi olan 225 hasta alındı. Epilepsi tanısı, iki veya daha fazla provoke olmayan nöbet öyküsü ile kondu. Tüm olguların demografik özellikleri, günlük alınan levetirasetam dozu, önceden aldığı antiepileptik ilaçlar, nöbet şekli, nöbet etiyojisi, ilaç yan etkisi kaydedildi.

Bulgular: Çalışmaya 95'i kız, 130'u erkek, toplam 225 hasta alındı. Hastaların 125'inde (%55.6) jeneralize, 90'unda (%40) fokal, 10'unda (%4.4) da diğer nöbet vardı. Olguların 186'sında (%82.7) nöbet sonlandı. Fokal ve jeneralize nöbeti olan hastalarda levetirasetam etkinliği açısından fark bulunmadı. Hastaların 18'inde (%8), en sık hırçınlık ve sinirlilik olmak üzere, yan etki gelişti. Yan etki ile ilaç dozu arasında ilişki bulunmadı.

Sonuç: Levetirasetam monoterapisi, çocukluk çağı epilepsilerinde görülen fokal ve jeneralize nöbetlerin tedavisinde etkindir. İlaç kesmeyi gerektirmeyecek kadar hafif ve geçici yan etkisi olması sebebi ile iyi tolere edilmektedir.

Anahtar sözcükler: Çocuk; etkinlik; epilepsi; levetirasetam; monoterapi; güvenilirlik.

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Introduction

Epilepsy is a common neurological disorder in the pediatric population, affecting up to 1% of children, for whom the mainstay of treatment is anticonvulsant medication.^[1] Control of abnormal neuronal activity with antiepileptic drugs (AEDs) is accomplished by elevating the threshold of neurons to electrical or chemical stimuli, or by limiting propagation of seizure discharge from its origin.^[2] The choice of an AED for treatment of epilepsy in infants and children depends not only on efficacy of the agent, but also on safety, impact on behavior and learning, and existing patient co-morbidities.^[3] Despite frequent use of anticonvulsant drugs, remarkably little is known about the safety and efficacy of these medications in the pediatric epilepsy population.

Levetiracetam (LEV) is second-generation antiepileptic drug that has been approved for treatment of epilepsy in both children and adults.^[4] The mechanism of action differs structurally and functionally from other currently available AEDs, as it binds to synaptic vesicle protein 2A (SV2A). Presence of SV2A in the presynaptic terminals suggests that its antiepileptic function might be based on affecting presynaptic events that regulate synaptic vesicle release.^[5] Although precise mechanism of action is not known, Nowack et al.^[6] suggested that LEV might modulate SV2 protein interactions. As a consequence, normal levels of SV2 and synaptotagmin (an SV2-binding protein) at the synapse are maintained, which may reduce seizures. It also plays a role in free calcium (Ca²⁺) homeostasis by inhibiting ryanodine and inositol 1,4,5-trisphosphate receptor-dependent Ca²⁺ release from endoplasmic reticulum and by inhibiting Ca²⁺ entry through blocking of the L-type Ca²⁺ channels in hippocampal neurons.^[7] LEV treatment in children has proven efficacy with localization-related and generalized epilepsies.^[8-11]

The aim of this study was to evaluate the effectiveness of LEV in different types of pediatric epilepsy and its possible side effects.

Materials and Methods

Participants in this study were retrospectively identified from the İnönü University Faculty of Medicine clinical database. Study population comprised series of children aged from 1 month to 18 years who were treated with LEV

between 2013 and 2015, and for whom at least 1 year of clinical follow-up was available. Detailed medical and family histories were obtained in addition to neurological examinations and neurophysiological tests. Systemic and neurological examinations were performed by pediatric neurologist. All cases were carefully evaluated for presence of seizure. Seizure type and epilepsy syndromes were classified according to International League Against Epilepsy (ILAE) 2016 classification.^[12] Seizure type was determined according to history obtained from parents and seizures witnessed during examinations. Routine electroencephalography (EEG) evaluations were performed with electrodes placed according to the international 10–20 system.

Patients were included in the study if:

- they had experienced at least 1 seizure with corresponding clinical event and EEG abnormality,
- they had experienced at least 2 seizures with corresponding clinical event in the last 6 months, or
- they were epileptic patients taking any antiepileptic drug (monotherapy) without seizure control.

General therapeutic strategy was to titrate dose of LEV until patients were seizure-free, reported experiencing adverse effects requiring discontinuation of therapy, or the treating physician determined drug to be ineffective. Estimates of seizure frequency and occurrence of side effects were based on parental report. For all patients, average daily dose of LEV was calculated as weighted average based on relative duration of therapy for each individual dose. Study patients were divided into 2 groups; the first group consisted of patients taking LEV as first monotherapy, and second group comprised patients who had previously used different AED as monotherapy. Initial dose was 10 mg/kg/day twice daily. If dose was well tolerated but there was insufficient seizure control, dose could be increased by 10 mg/kg/day for 2 weeks, with maximum dose of 60 mg/kg/day. Patients were called for follow-up 1 month after initiation of treatment and every 3 months afterward. Frequency of seizures, drug dose, drug neglect, and side effects were recorded at each follow-up visit. Patients were divided into 4 groups according to treatment response: termination of seizures, >50% reduction in seizures, <50% reduction in seizures, and no response.

Occurrence of adverse events was evaluated with help of standardized side effect questionnaire, and possible re-

Table 1. Seizure type, etiology, and treatment response

	Termination of seizures	>50% reduction in seizures	<50% reduction in seizures	No response
Seizure type				
Generalized	101/125 (80.8%)	4/125 (3.2%)	12/125 (9.6%)	8/125 (6.4%)
Focal	79/90 (87.8%)	4/90 (4.4%)	3/90 (3.3%)	4/90 (4.4%)
Other	6/10 (60%)	0	2/10 (20%)	2/10 (20%)
Etiology				
Symptomatic	62/76 (81.6%)	3/76 (3.9%)	7/76 (9.2%)	4/76 (5.3%)
Cryptogenic	5/8 (62.5%)	0	1/8 (12.5%)	2/8 (25%)
Idiopathic	119/141 (84.4%)	5/141 (3.5%)	9/141 (6.4%)	8/141 (5.7%)

Table 2. Drug dose and treatment response

	n=225		Levetiracetam <30 mg/kg/d (n=151)		Levetiracetam >30 mg/kg/d (n=74)	
	n	%	n	%	n	%
Termination of seizures	186	82.7	129	85.4	57	77
>50% reduction in seizures	8	3.6	6	4	2	2.7
<50% reduction in seizures	17	7.6	9	6	8	10.8
No response	14	6.2	7	4.6	7	9.5

Table 3. Cranial MRI findings

	n	%
Normal	140	62.2
CNS developmental abnormality	33	14.7
Hypoxic ischemic encephalopathy	17	7.6
Periventricular leucomalacia	15	6.7
Metabolic disease	6	2.7
Trauma	3	1.3
Other	11	4.9
Total	225	100

MRI: Magnetic resonance imaging; CNS: Central nervous system.

relationship between each complaint and LEV therapy was evaluated by the treating physician. Questionnaire contained queries covering presence and severity of behavioral changes, sleep-related problems, and physical problems. Seizure and epileptic syndromes were classified according to operational classification of the ILAE.^[12]

This report was approved by the ethics committee of İnönü University Faculty of Medicine.

Results

Total of 225 patients, 95 girls and 130 boys, were enrolled in the study. Age of patients ranged from 1 month to 18 years.

Mean age was 8.41 ± 4.96 years among females and 7.4 ± 4.34 years among males. Seizure type and response to treatment according to etiological classification are provided in Table 1. Before LEV was administered, patients underwent EEG, and 173 (76.9%) of the patients exhibited abnormal results. Total of 123 (54.7%) patients had focal discharges, 50 (22.2%) patients had generalized discharges, and 52 (23.1%) patients had normal EEG. In annual follow-up, both generalized and focal seizures had stopped at rate of 80.8% and 87.8%, respectively.

At 1-year follow-up, 82.7% of patient seizures had terminated. When LEV dose and treatment response were compared, it was observed that 30 mg/kg/day dose was effective (Table 2). Total of 37.8% (85/225) of the patients who underwent magnetic resonance imaging (MRI) displayed different findings. Most common finding on MRI was malformation of cortical development (14.7%) (Table 3).

When patients were divided into subgroups according to age, it was seen that in group with diagnosis of epilepsy >1 year old, AED dose was lower ($p=0.009$). There was no difference in terms of seizure control between patients using LEV monotherapy as first drug and the group that had previously used different AEDs (Table 4). AED characteristics of drugs used before LEV can be seen in Table 5.

Table 4. Comparison of therapeutic response of the group that used LEV for the first time and the group that had used another AED before

	First monotherapy (n=114)		Previous AED (n=111)		Total (n=225)	
	n	%	n	%	n	%
Termination of seizures	101	88.6	85	76.6	186	82.7
>50% reduction in seizures	5	4.4	3	2.7	8	3.5
<50% reduction in seizures	4	3.5	13	11.7	17	7.5
No response	4	3.5	10	9	14	6.2

LEV: Levetiracetam; AED: Antiepileptic drug.

Table 5. AEDs used before LEV

	n	%
First monotherapy	114	50.7
Previous antiepileptic drugs used	111	49.3
Valproic acid	44	39.6
Carbamazepine	14	12.6
Phenobarbital	22	19.8
Valproic acid, carbamazepine	17	15.3
Oxcarbazepine	3	2.7
Phenobarbital, valproic acid	6	5.4
Valproic acid, carbamazepine, oxcarbazepine	5	4.5
Total	225	

In 8% of cases, drug-related side effects were seen. Most common side effects were irritability and nervousness (Table 6).

Discussion

Monotherapy treatment of epilepsy has many potential benefits over polytherapy, including lower toxicity, fewer adverse events, increased compliance, reduced treatment costs, and lower potential for drug-drug interactions.^[13]

LEV is known to be effective in combined treatment of focal epilepsy, but little is known about its effect in monotherapy. Lagae et al.^[10] were the first to report prospective trial on LEV monotherapy in children. Many retrospective studies on LEV monotherapy in children have subsequently been published.^[14–20] Most included patients with focal and/or generalized epilepsy. Levetiracetam dosage in these studies ranged from 10 to 108 mg/kg/day, but was usually in 20 to 40 mg/kg/day range. Mean duration of follow-up ranged from 3 to 27 months.^[16,17,19,20]

Levetiracetam efficacy was considered to be good, and seizure freedom was achieved in more than 60% of patients in most studies, including those on children who had been using another AED prior to LEV monotherapy.^[21] In our study, response was better among the children who were AED-naïve before initiating treatment with LEV, and we ascertained that it was effective in 82.7% of all cases. There was no difference in effectiveness of the drug between patients with focal and generalized seizures. Lagae et al.^[10] also obtained similar efficacy results for the drug in partial and generalized seizures. Their previous studies stand particularly on LEV's strong effect on partial seizures and possible

Table 6. Side effects and dosage

Side effect	Levetiracetam <30 mg/kg/d (n=151)		Levetiracetam >30 mg/kg/d (n=74)		n=225	
	n	%	n	%	n	%
Irritability, nervousness	6	3.9	2	2.7	8	3.6
Allergy	1	0.7	0	0	1	0.4
Forgetfulness	2	1.3	1	1.4	3	1.3
Increased number of seizures	2	1.3	1	1.4	3	1.3
>10% weight gain	1	0.7	1	1.4	2	0.9
Somnolence	1	0.7	0	0	1	0.4
Total	13	8.6	5	6.8	18	8

effect on generalized seizures.^[22] In addition, we compared response to treatment according to etiological classification and observed that it was more effective in idiopathic group. There is not sufficient data in the literature demonstrating relationship between efficacy of the drug and etiological classification of seizures.

Tolerability was good in all studies, with behavioral and cognitive changes being most common adverse events; discontinuation rate due to adverse events was low (0–12%).^[21] Side effects seen are reported to occur in the first 5 months of treatment in 17.2% to 51.3% of patients. Most common side effects are related to the central nervous system.^[23]

Side effects were seen in 8% of our patients, and in 3, use of drug was discontinued. Side effects disappeared or decreased with drug dose reduction in remaining patients. Most common side effects were nervousness and irritability. In our study, there was no significant relationship between drug dose and side effects. In study of 200 children with refractory epilepsy, it was demonstrated that side effects were independent of drug dose. Rate of 6.7% to 43% seizure increase during LEV treatment has been reported.^[24,25] Only 1.3% of our patients needed to discontinue drug due to increase in number of seizures.

In summary, LEV seems to be tolerable and effective in seizure control, with only a few adverse events that were mostly transient, even in very young children and in dosages up to 60 mg/kg/day.

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