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The efficacy, tolerability and safety of levetiracetam therapy in a pediatric population

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ABSTRACT

Purpose: The purpose of this study was to assess the efficacy and safety of levetiracetam monotherapy in a pediatric population.
Method: A retrospective review was performed of the charts of 351 consecutive children who were 6 months to 18 years of age and were treated with levetiracetam. Levetiracetam monotherapy was initiated and dosed to efficacy or unacceptable side effects, with a range of 10–112 mg/kg/day. Electroencephalographic examination was performed at pre-treatment and 12th months in the post-treatment period. Following the commencement of levetiracetam treatment, the retention rate at 3, 6 and 12 months was 100%, 75% and 57%, respectively.
Results: The monotherapy retention rate at 3 and 12 months following the commencement of levetiracetam treatment was (231/351, 66%), and (126/200, 63%) respectively. A total of 165 (47%) patients had idiopathic epilepsy and 186 patients (53%) had symptomatic-cryptogenic epilepsy. The >90% seizure reduction rate was 65%, and the 50–90% seizure reduction rate was 14% at the 3rd month of treatment. Similarly, the >90% seizure reduction rate was 63%, and the 50–90% seizure reduction rate was 15% at the 12th month of treatment. EEG improvement (normalization of EEG) was observed in 65 (47%) patients. Overall, 61 (17%) patients showed adverse events. The most reported side effects were irritability (67%), hyperactivity (8%), somnolence (6%), behavioral disorders (5%), restlessness (5%), increased seizure frequency (3%), enuresis (2%), headache (2%) and attempted suicide (2%).
Conclusion: The retrospective study of 231 consecutive pediatric patients to confirm that levetiracetam is effective as initial monotherapy for different types of seizures and/or epilepsy syndromes. However there is still a need for well-designed trials to justify the widespread use of levetiracetam monotherapy in children with specific epilepsy syndromes.

1. Introduction

Levetiracetam is thought to have broad-spectrum efficacy, and because it lacks significant pharmacodynamics interactions with other antiepileptic drugs, levetiracetam is an attractive choice for the treatment of seizures associated with childhood epileptic disorders [1,2].

In recent years, open-label studies that have examined the use of levetiracetam as an adjunctive therapy in pediatric populations have reported response rates (a reduction in seizure frequency of at least 50%) ranging from 20 to 60%[3–9]. Levetiracetam monotherapy was well tolerated in these studies, and few adverse events were reported. Although levetiracetam has demonstrated efficacy as adjunctive therapy in children with epileptic disorders, limited data have been reported regarding its use as monotherapy [10–26]. Additional clinical studies are needed identify the optimal dosage and to define the efficacy, tolerability and safety of levetiracetam as a monotherapy and its effects on specific epilepsy syndromes.

In the present study, we retrospectively evaluated the efficacy, tolerability and safety of levetiracetam therapy in a large cohort of children (6mo to 18y) with epileptic disorders.

2. Materials and methods

The subjects for this study were retrospectively identified from the medical records of the Children's Hospital of Katip Çelebi

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University and the private office records of an author (H.T.) via ICD-9 code searches (345.x seizure). The study population comprised a consecutive series of 351 children who were treated with levetiracetam between 2005 and 2015 and for whom ≥12 months of clinical follow-up data were available. The demographic, clinical, electroencephalographic (EEG) and magnetic resonance imaging (MRI) findings were recorded. Patient diaries and detailed histories were used to calculate the seizure frequencies as accurately as possible.

The seizure types, etiologies and epileptic syndromes were classified according to the International League Against Epilepsy Proposal for Revised Classification of Epilepsies and Epileptic Syndromes [2]. The patients were clinically evaluated at 3, 6 and 12months. Electroencephalographic features were evaluated at pre-treatment and at 6–12 months during the post-treatment period. An EEG improvement was defined by a pre-treatment EEG that was abnormal and a second EEG that was normal (no spikes or abnormalities). The initial dose of 10 mg/kg/day was increased in 2-week steps of 10 mg/kg/day when necessary up to the maximum dose of 110 mg/kg/day. The blood levels of drug were not collected from the patients. The retention rates for the levetiracetam treatment were recorded for the cohort and the monotherapy group. The clinical responses were graded as complete or partial responses at the 3rd and 12th months of treatment. Complete responses were defined by seizure frequency reductions of 90% or more, and partial-responses were defined by seizure frequency reductions ranging from 50 to 90%. The tolerability and adverse events were assessed by documenting the adverse events that were spontaneously reported by the parents or the children. In the presence of formal psychological tests, the degree of intelligence was defined according to intelligence quotient (IQ) test results. In the absence of formal tests, based on the available information, the degree of cognitive deterioration or improvement was defined according to the clinical judgment of the authors (HT, PG, and NOD).

The database was created and analyzed using SPSS statistical software (version 15.0; Chicago, IL, USA) for Windows. Frequencies and percentages were used to summarize the categorical data, and the continuous data were summarized using the mean and standard deviation (SD) or the median and interquartile range (IQR, Q_{75}–Q_{25}). The data analyses were performed with Pearson X^2 tests for the categorical variables and Student's t test for the continuous variables. p values below .05 were considered statistically significant. Multivariate logistic regression analysis was used to evaluate the adverse events.

This study was approved by the Local Ethics Committee of the Medical School, Katip Çelebi University.

3. Results

3.1. Patients characteristics (Table 1)

A total of 351 children (210 boys and 141 girls) were enrolled in this study. The median patient age was 9.88 years (IQR, 10.12 years; range, 6 months to 18 years, 25% = 4.51 and 75% = 14.61). A total of 165 patients (47%) had idiopathic epilepsy, and 186 (53%) had symptomatic-cryptogenic epilepsy. In total, 204 (58%) patients had generalized type seizures, and 147 (42%) patients had partial seizures. The majority of the patients (n = 331, 94%) had undergone magnetic resonance imaging (MRI), and 139 (42%) of the images revealed abnormal results that included encephalomalacia (n = 53), cortical dysplasia (n = 27), pachygyria (n = 1), polymicrogyria (n = 1), periventricular leukomalacia (n = 22), cerebral atrophy (n = 17), delayed myelination (n = 10), leukodystrophy (n = 6), mesial temporal sclerosis (n = 1) and a dysembryoplastic neuroepithelial tumor (n = 1). The possible underlying causes of epilepsy were determined in 148 (42%) patients. Forty-seven (32%) patients had hypoxic ischemic encephalopathy, 29 (26%) patients had neurometabolic disorders (e.g., neuronal ceroid lipofuscinosis), 29 (20%) patients had neurodevelopmental disorders (e.g., cortical dysplasia), 22 (15%) patients had prematurity, seven (5%) patients had genetic disorders (e.g., Angelman syndrome, tuberous sclerosis), seven (5%) patients had histories of central nervous system infections, and seven (5%) patients had posttraumatic epilepsy. Attention deficit hyperactivity disorder (ADHD) was accompanied by epilepsy in 38 (11%) patients, and autistic spectrum disorders were accompanied by epilepsy in 16 (5%) patients. Before the patients were administered levetiracetam, the majority had undergone electroencephalography (n = 343, 98%), and 240 (68%) of the patients exhibited abnormal results. A total of 182 (76%) patients had focal discharges, 34 (14%) patients had generalized discharges, and 24 (10%) patients had multifocal discharges. Second EEGs were performed for 138 (39%) patients, and 65 (47%) patients demonstrated improvement. The mean daily doses of levetiracetam were <30 mg/kg in 141 (40%) patients, 30–50 mg/kg in 161 (46%) patients, 60–80 mg/kg in 40 (11%)

Table 1
Demographic and clinical characteristics of cohort (n = 351).

Median age (IQR, Q_{75}–Q_{25})	9.88 (IQR, 10.12)	Psychiatric disorders	n (%)
Gender	n (%)	ADHD	38 (11%)
Female	210 (60%)	Autism spectrum disorder	16 (5%)
Male	141 (40%)	Pre-treatment EEG findings (n = 343, 98%)	
Type of epilepsy		Abnormal	240 (68%)
Idiopathic	165 (47%)	Normal	103 (30%)
Symptomatic-cryptogenic	186 (53%)	Pre-treatment EEG findings	
Seizure semiology		Generalized	34 (14%)
Generalized	204 (58%)	Focal	182 (76%)
Partial	147 (42%)	Multifocal	24 (10%)
MRI (n = 331, 94%)		Improvement on EEG (n = 138, 39%)	
Normal	192 (55%)	Yes	65 (47%)
Encephalomalacia	53 (15%)	No	73 (53%)
Cortical dysplasia	27 (8%)	Mean daily dose (mg/kg/day)	
Pachygyria	1	<30	141 (40%)
Polymicrogyria	1	30–59	161 (46%)
Periventricular leukomalacia	22 (6%)	60–80	40 (11%)
Cerebral atrophy	17 (5%)	>80	9 (3%)
Delayed myelination	10 (3%)	Mental retardation	
Leukodystrophy	6 (2%)	Yes	123 (35%)
Mesial temporal sclerosis	1	No	228 (65%)
Dysembryoplastic neuroepithelial tumor	1		

IQR: interquartile range, ADHD: attention-deficit hyperactivity disorder, EEG: electroencephalography.