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Efficacy and Safety of Levetiracetam for Childhood Epilepsies

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ABSTRACT

Background: Levetiracetam (LEV) is a broad spectrum second-generation antiepileptic drug (AED). **Objective:** The objective of the study was to investigate the efficacy and safety of levetiracetam for childhood epilepsies. M**ethods**: This is single, tertiary centre observational, prospective study, that included paediatric patients who were treated with levetiracetam at Paediatric hospital University Clinical Centre Sarajevo, during the period of 15 years (2008-2022). Inclusion criteria were: paediatric patients age > 1 month, diagnosed with epilepsy according to International League Against Epilepsy. After the introduction of levetiracetam, each patient has been followed up at least 12 months. According to the outcome the patients were divided into 5 groups: seizure reduction >50%, seizure reduction <50%, complete seizure freedom, the same number of seizures and increased number of seizures. From these groups two intergroups have been formed: responders (seizure reduction >50% and complete seizure freedom) and non-responders (seizure reduction <50%, the same number of seizures and increased number of seizures). **Results** The study enrolled 259 patients (141 female and 118 male), with mean age 7 years (3,0–12.0). Comorbidities were present at 129/259 (49.8%) patients. After 12 months of treatment, 25/259 (9.7%) patients had seizure reduction >50%, 30/259 (11.6%) patients had seizure reduction <50%, 154/259 (56.5%) patients had achieved seizure freedom, 31/259 (12%) patients had same number of seizures, while 19/259 (7.3%) patients had increased number of seizures. Seizure frequency between responders and non-responders, before treatment and after 12 months of treatment was statistically significant (p<0.001). **Discussion:** Non responders had the best outcome with ditherapy (30/79; 38%), while responders had the best outcome with monotherapy (161/180;89.4%). **Conclusion:** Levetiracetam is efficient antiepileptic drug for different types of epilepsies in childhood, used as mono, di or polytherapy.

Keywords: epilepsy, levetiracetam, efficacy, safety.

1. BACKGROUND

Epilepsy is one of the most common neurological diseases in childhood. The aims of adequate treatment are seizure freedom, if possible, and improvement of quality of life for patients and their families.

Levetiracetam (LEV) is a broad spectrum second-generation antiepileptic drug (AED), structural analogue of piracetam. Its mechanism of action is modulation of neurotransmitter release through binding to the synaptic vesicle glycoprotein SV2A (1, 2). SV2A is an integral membrane protein found in the vesicles of almost all synaptic terminals, regardless of neurotransmitter content and its expression is similar on both glutamatergic and GABAergic terminals (3, 4). LEV also modulates AMPA receptor channels, with result of decreased kainate and AMPA -induced excitatory currents (5).

After the FDA approval of levetiracetam in 1999, the proportion of patients with epilepsy who were treated with LEV has increased rapidly due to better tolerability and an improved efficiency compared to other AED (3). Today, it is one of the most prescribed AED, due to its favourable efficacy and few drug-drug interactions. Several clinical trials confirmed its efficacy for multiple seizure types , status epilepticus and electrical status epilepticus during slow-wave sleep (ESES) (5). Besides antiepileptic effect, LEV also has antiepileptogenic, neuroprotective, anti-inflammatory and anti-oxidant effects (3). LEV binds to plasma proteins less than 20% and does not affect the protein binding of other drugs (3). It readily crosses blood-brain barrier and its CSF half-life is 3 time longer than that for plasma. It is metabolized predominantly

by nonhepatic hydrolysis and reminder is excreted by kidneys unchanged (6). It makes it useful in patients with hepatic dysfunction and it is independent of the hepatic cytochrome p450 (CYP450) system (3). Therapeutic drug monitoring of levetiracetam is generally unnecessary (9). The most common side effects are drowsiness, dizziness, headache, fever, dry mouth, asthenia and behavioural changes.

There are no relevant pharmacokinetic interactions between levetiracetam and other antiepileptic drugs.

2. OBJECTIVE

The objective of the study was to investigate the efficacy and safety of levetiracetam for childhood epilepsies.

3. PATIENTS AND METHODS

This is single, tertiary center observational, prospective study, that included pediatric patients who were treated with levetiracetam at Pediatric hospital Clinical Center University of Sarajevo, during the period of 15 years (2008-2022).

Inclusion criteria were: pediatric patients age > 1 month, treated with levetiracetam, diagnosed with epilepsy according to guidelines from International League Against Epilepsy. After the introduction of levetiracetam, each patient has been followed up at least 12 months, with regular checkups each 3 to 4 months. For each patient, several demographic and clinical data were collected: age, gender, age of epilepsy diagnosis, epilepsy semiology, type of comorbidity, duration of therapy, therapeutic modality (monotherapy or polytherapy), frequency of seizures before and 12 months after the introduction of levetiracetam, brain MRI and side effects of the drug. Drug levels were not monitored for patients included in the study. The frequency of seizures before the introduction of levetiracetam therapy was defined by the number of seizures according to the scheme: less than five seizures, five to ten seizures, more than ten and complete absence of seizures.

Based on the clinical response and after 12 months of using the LEV, the evaluation of the number of seizures was performed, on the basis of which the patients were divided into 5 groups: reduction of seizures by more than 50%, reduction of seizures by less than 50%, complete absence/elimination of seizures, number of seizures without significant changes and worsening/increased number of seizures. Patients by whom there was a reduction of seizures by more than 50% and complete elimination of seizures were defined as the subgroup of responders, the rest were classified in the subgroup of non-responders.

All patients had a brain MRI that was classified as normal or pathologically changed. Adverse effects of the drug and its tolerability were recorded based on clinical monitoring and reporting by patients and their parents, and most often manifested as drowsiness and irritability.

Sex male– 141 (54.4%); female– 118 (45.6%)
Median age (years) – 7.0 (3.0-12.0)
Seizure type:
generalized clonic tonic 172/259 (66.4%)
focal attacks in 58/259 (22.4%)
absences in 2/259 (0.8%)
myoclonic in 2/259 (0.8%)
focal with transition to bilateral tonic-clonic 18/259 (6.9%)
generalized myoclonic 5/259 (1.9%)
focal-myoclonic, atonic in 2/259 (0.8%)
Comorbidities Yes – 129 (49.8%), No – 130 (50.2%)
Type of comorbidity
Cerebral palsy – 14/129 (5.4%)
Neurologicall at-risk child – 1/129 (0.4%)
Encephalopathy 23/129 (8.9%)
Developmental brain anomaly 18/129 (6.9%)
Autism and pervasive disorders 12/129 (4.6%)
Condition after CNS infections 9/129 (3.5%)
Metabolopathy 6/129 (2.3%)
Other – 46 (17.8%)
Duration of LEV treatment (years) – 4.0 (2.5-6.0)
Therapy
Monotherapy– 181/259 (69.9%)
Ditherapy– 44/259 (17.0%)
Politherapy – 32/259 (12.4%)
Seizure frequency before LEV treatment
>10 – 73/259 (28.2%)
5 do 10 – 29/259 (11.2%)
< 5 – 153/259 (59.1%)
No seizures – 4/259 (1.5%)
Seizure frequency after 12 months of LEV treatment:
>50% - 25/259 (9.7%)
<50% - 30/259 (11.6%9
No seizures – 154/259 (56.5%)
Same number of seizures – 31/259 (12.0%)
Increased number of seizures – 19/259 (7.3%)
Brain MRI Normal – 143/259 (55.2%), Pathological 116/259 (44.8%)
Side effects Yes – 3/259 (1.2%), No – 256/259 (98.8%)

Table 1. Baseline characteristics

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 21.0. The data were presented as absolute value (N), percentage (%), and the median and interquartile range (25th–75th percentiles). The significance of the divergence from the normal distribution was assessed using the Kolmogorov-Smirnov tests. The Mann-Whitney U-test were used to compare the groups based on the distribution of variables. The $\chi 2$ and Fisher's exact tests were used to analyze the dependence between categorical variables. A $p<0.05$ was considered statistically significant

4. RESULTS

A total number of 259 patients (141 female and 118 male) were included in the study. All the demographic and clinical data of patients are summarized in Table 1.

As a starting parameter of the efficacy of levetiracetam, patients were divided into four groups, according to the frequency of seizures before the introduction of therapy. The first group included patients with more than ten seizures (73/259; 28.2%), the second group included patients with 5 to 10 seizures (29/259; 11.2%),

Variable	Non responders (n=79)	Responders (n=180)	P
Male Female	42/79 (53.2%) 37/79 (46.8%)	99/180 (55.0%) 81/180 (45.0%)	0.785
Mean age (years)	5.0 (2.0-10.0)	8.0 (4.0-12.0)	0.001
Seizure type			
Generalized tonic-clonic Focal Absence Myoclonic Focal with transition to bilat.tonic-clonic Focal+myoclonic+atonic Generalized tonic-clonic +myoclonic	46/79 (58.2%) 19/79 (24.1%) 1/79 (1.3%), 1/79 (1.3%) 6/79 (7.6%) 2/79 (2.5%) 4/79 (5.1%)	126/180 (70.0%) 39/180 (21.7%) 1/180 (0.6%) 1/180 (0.6%) 12/180 (6.7%) 0 (0.0%) 1/180 (0.6%)	
Comorbidities	53/79 (67.1%)	77/180 (42.8%)	<0.001
Duration of LEV treatment (years)	5.0 (3.0-7.0)	4.0 (2.5-5.5)	0.069
Therapy modalities			
Monotherapy Ditherapy Politherapy	21/79 (26.9%) 30/79 (38.0%) 28/79 (35.1%)	161/180 (89.4%) 14/180 (7.8%) 5/180 (2.8%)	<0.001
Seizure frequency before LEV			
> 10 5 do 10 <5	43/79 (54.4%) 4/79 (5.1%) 32/79 (40.5%)	30/180 (16.7%) 25/180 (13.9%) 125/180 (69.4%)	<0.001
Brain MR pathological	46/79 (58.2%)	70/180 (38.9%)	0.004
Side effects	1/79 (1.3%)	2/180 (1.1%)	-

Table 2. Comparative analysis of demographic and clinical characteristics between non-responders and responders

the third group included patients who had less than 5 seizures (153/259;59.1%) and the fourth group included patients without clinically evident seizures (/259;1.5%).

After 12 months of treatment, 25/259 (9.7%) patients had seizure reduction >50%, 30/259 (11.6%) patients had seizure reduction <50%, 154/259 (56.5%) patients had achieved seizure freedom, 31/259 (12%) patients had same number of seizures, while 19/259 (7.3%) patients had increased number of seizures.

Results are presented as absolute numbers N and as percentage values, and as median and interquartile range (25-75 percentiles).

The comparative analysis of demographic and clinical characteristics between non-responders and responders subgroup is summarized in the Table 2.

There were no statistically significant differences in the gender distribution between the examined groups, as well as the length of levetiracetam administration. The median age in the group of non-responders was 5.0 (2.0-10.0) years, and in the group of responders 8.0 (4.0-12.0), and the determined difference was statistically significant (p<0.001). The established difference in the frequency of comorbidities between the examined groups was statistically significant (p<0.001). The difference in the representation of therapeutic modalities between the non-responders and responders was statistically significant (p<0.001). The difference in the frequency of seizures before the start of therapy between non-responders and responders was statistically significant (p<0.001). Pathological MRI of the brain was more frequent in non –responders group and difference between the examined groups was statistically significant (p<0.001).

Results are presented as absolute numbers N and as percentage values, and as median and interquartile range (25-75 percentiles).

5. DISCUSSION

Levetiracetam is a broad-spectrum anticonvulsant drug with an unconventional mechanism of action that can be used as monotherapy or adjunctive therapy for various types of epileptic seizures. Looking at its safety profile–the half-life of the drug, rapid absorption, metabolism that does not take place through the liver, minimal binding to plasma proteins, absence of interaction with other AET and passing through the blood-brain barrier, it proved to be one of the preferred antiepileptic drugs for use in the paediatric population (3).

Due to its effectiveness and good tolerance, levetiracetam has recently been increasingly used as a drug of first choice–monotherapy in the treatment of epileptic seizures, especially focal and bilateral clonic-tonic seizures. Numerous studies confirmed a significant reduction of seizures in children on polytherapy due to focal, myoclonic, generalized seizures and juvenile myoclonic epilepsy (10). It has also been shown to be effective treatment for patients in status epilepticus (11, 12).

To monitor the effectiveness of levetiracetam therapy, patients were divided into three groups: patients with monotherapy, ditherapy and polytherapy, with a com-

parison of responders and non-responders. Patients in both, responders and non-responders group responded positively to the registered modalities of therapy. In the non-responders group the best clinical response was to the ditherapy 30/79 (38.0%), and in the group of responders 161/180 (89.4%) to the monotherapy modality. The comparison between these groups showed a statistically significant difference (p<0.001) in favour of responders, where a smaller number of antiepileptic drugs was needed for better control of epileptic seizures, which is in accordance with studies that confirmed that the use of levetiracetam as monotherapy can be considered effective (13-15,18).

The largest number of patients included in our study generally had a satisfactory response to levetiracetam therapy. Seizure frequency before the initiation of levetiracetam was significantly higher in non-responders' group. Monotherapy was applied for 161/180 (89.4%) patients in responders' group and 21/79 (26.9%) patients in non-responders' group, with statistically significant difference in favour of responders (p<0.001). The positive response to therapy fits with studies where monotherapy with levetiracetam for at least one year led to a significant reduction or complete cessation of seizures, regardless of whether they were focal or generalized clonic tonic seizures (14,17,18).

The mean age of the patients in non-responders' group was 5.0 (2.0-10.0) years an in responders' group 8.0 (4.0-12.0) years which is statistically significant difference (p<0.001). Based on the obtained results, older patients responded better to therapy, which could be explained by the fact that epilepsy in children with comorbidities occurred earlier, and consequently, the response to therapy was weaker. In our study, in addition to diagnosed epilepsy, the existence of comorbidities in children was monitored. The most common comorbidities were developmental anomalies of the CNS, cerebral palsy, autism and the condition after an infection of the central nervous system. The results showed that there was a statistically significant difference (p<0.001) in the frequency of comorbidities in non-responders' group (53/79; 67.1%) compared to responders' group (44/180; 42.8%). Children with comorbidities generally had a poorer response to treatment with levetiracetam, either as monotherapy or polytherapy, in contrast to certain studies in which levetiracetam was documented to have satisfactory efficacy in the treatment of epileptic seizures in children with comorbidities (19,20). Although it is generally more difficult to obtain satisfactory seizure control in this group of children, the use of polytherapy including levetiracetam has proven to be effective (21).

All patients included in the study had done brain MRI. Normal findings had 143/259 patients (55.2%), while pathologically altered brain MRI was detected in 116/259 (44.8%) patients.

The pathological brain MRI was present in 46/79 (58.2%) patients of non-responders' group and 70/180 (38.9%) patients of responders group. There is statistically significant difference between these groups in favour of non-responders' group (p 0.004), which fits in with the study where the epilepsies with pathologically altered brain MRI , gave a weaker response to antiepileptic therapy (22).

There are studies on new methods in radiological diagnostics, such as diffusion tensor imaging (DTI), which in the future could be used as a predictive indicator of the success of levetiracetam therapy. This would undoubtedly contribute to the development of personalized therapy and patient screening (23).

In our study all patients were monitored for possible side effects of levetiracetam. The most frequently reported side effects in similar studies were somnolence, nausea, instability, hyperactivity, aggressiveness, anxiety, depression, psychosis and suicidal ideation. These side effects were more prevalent than in our study, where the minimal number of side effects was reported. Side effects were noted only in 3 cases: two patients in the responders' and only one patient in non-responders' group (24, 25).

6. CONCLUSION

Levetiracetam has proven to be a very effective antiepileptic drug in the treatment of various types of epilepsy in children, whether it is used as mono, di or polytherapy. It has a satisfactory effect in the treatment of epilepsies in children with comorbidities. Due to the small number of side effects related to its use, it can be considered a drug with a very high safety profile, which allows the use of levetiracetam in all age groups.

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