RESEARCH ARTICLE

THE EFFICACY AND SAFETY OF ZONISAMIDE AS AN ADD-ON DRUG IN THE TREATMENT OF LENNOX–GASTAUT SYNDROME

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Abstract

Objective

The Lennox-Gastaut syndrome (LGS: the triad of intractable seizures of various types, a slow spike-wave pattern in EEG and mental retardation) is one of the most difficult epilepsy syndromes to treat. The aim of this study was to evaluate the efficacy and safety of zonisamide (ZNS) as add-on therapy in seizures of children with LGS.

Materials & Methods

In a quasi- experimental study, seizure frequency and side effects of 40 children with LGS who were referred to the pediatric neurology clinic of Shaheed Sadoughi University of Medical Sciences, Yazd, Iran, between September 2008 and November 2009 and were on ZNS for six months were evaluated.

Results

Twenty one boys and 19 girls with a mean age of 6.6 ± 3.6years were evaluated. At the end of six months of treatment with ZNS, 25% became seizure free, 25% had > 50% reduction in seizure frequency while 35% did not have a notable change in seizure frequency and 15% experienced an increase in seizure frequency.

Drug was effective in 62.5% of the myoclonic and generalized tonic-clonic, 50% of the atonic, 43% of the mixed type and 33.4% of the tonic seizures.

Transient side effects were seen in 25% of the patients: drowsiness in 10%, hyperthermia in 5 % and irritability, fatigue, ataxia and anorexia (each one) in 2.5% of the patients. No serious side effects were reported.

Conclusion

ZNS could be considered as an add-on therapy in the management of intractable epilepsy in LGS.

Keywords: Lennox-Gastaut syndrome (LGS), Zonisamide, Epilepsy, Refractory epilepsy

Introduction

Lennox-Gastaut syndrome (LGS) is one of the catastrophic epileptic syndromes of childhood. William Lennox described the clinical features of the syndrome in 1930s (1). This syndrome is characterized by the triad of intractable seizures of various types, psychomotor retardation and a slow (less than 2.5-hertz) spike-wave pattern in the waking electroencephalogram (EEG) and fast rhythmic bursts during sleep. LGS accounts for 1-10 percent of all cases of childhood epilepsy but is a major contributor to morbidity and seizures are often associated with falls and injuries (2). The onset of the seizures varies from 6 months to 16 years of age (3).

Etiologic classification of LGS includes:

1. Symptomatic: with identifiable prenatal, perinatal, and postnatal causes

2. Idiopathic: with an unknown underlying cause in detailed investigations with normal psychomotor development at the onset of seizures. The term idiopathic has traditionally been used as cryptogenic (4).

Medical management of LGS is often difficult and seizures are mainly drug resistant. The cornerstone of treatment is antiepileptic drugs (AEDs), but other treatment methods of refractory seizures, including the ketogenic diet, intravenous immunoglobulin and surgical options (vagus nerve stimulation, corpus callosotomy, stereotactic surgical implantation of electrodes to the centromedian nuclei of the thalamus, etc.), may be used, as well. Different old and new AEDs such as benzodiazepines, carbamazepine, phenobarbital, primidone, phenytoin, valproate, zonisamide, topiramate, lamotrigine, felbamate, rufinamide, and levetiracetam have been used in LGS treatment. No single treatment regimen could be considered superior to others, and no study to date has shown one drug to be highly efficacious (4-6).

Zonisamide (ZNS) is one of the broad spectrum AEDs which may be effective in pediatric partial and generalized seizures, especially for myoclonic epilepsies. Its effect is based on the following mechanisms:

a) blocking voltage-dependent sodium channels

b) blocking T-type calcium channels

c) blocking potassium-evoked glutamate responses

d) scavenging hydroxyl and nitric oxide radicals

e) increasing gamma-aminobutyric acid release from the hippocampus

f) inhibition of erythrocyte carbonic anhydrase (4,5,7,8)

ZNS can be considered as a second-line drug in the treatment of infantile spasms, LGS and juvenile myoclonic epilepsy (9). The drug, as monotherapy or add - on therapy and in different dosages (1-20 mg/kg/day), has been used in the management of all seizure types and many epileptic syndromes of children in the United States, England, Japan, Korea, Italy, etc (7, 8, 10 - 15).

Since ZNS usage is less frequent and little information is available regarding its efficacy in various epileptic syndromes in Iran, we decided to evaluate the efficacy and safety of Zonisamide in all seizure types of children with LGS in Yazd, Iran.

Materials &Methods

This quasi-experimental (before and after) study was conducted on children with LGS and refractory epilepsy who were referred to the pediatric neurology clinic of Shaheed Sadoughi University of Medical Sciences between September 2008 and November 2009 in Yazd, Iran.

Sample size was assessed to be 40 persons based on Z formula and a confidence interval of 95% with 80% power, S= 30 and d=15 to detect any significant difference between the two groups with a level of 0.05.

The diagnostic criteria for the LGS in this study were based on International League Against Epilepsy (ILAE) classification (16). In fact, patients were considered as control group before, and case group after ZNS treatment. Care was taken to include LGS patients aged 1-18 years who had not responded to an adequate dosage of at least two conventional AEDS in single or combination, had at least one seizure in a week, were not sensitive to sulfonamide derivative, had not used ZNS formerly and maintained on ZNS for six months.

Variables such age, sex, age at seizure onset, type and frequency of seizures (based on history), etiologic classification, family history of epilepsy in first and second degree relatives (based on history and direct interview with children's parents) and brain MRI results were reviewed. The trial had three phases as follows:

1. Baseline phase: Seizure frequency per week in three months before adding ZNS was recorded.

2. Titration phase: To minimize the side effects of the drug, ZNS was added to the previous AEDs regimen in a four-week period as follows: 4, 8, 12, 16 mg/kg/day in two divided doses.

3. Maintenance phase: Maximum dose or the one which controlled seizures continued for six months. No new AEDs were added to ZNS and concomitant drugs, but concomitant antiepileptic drugs were administered at sufficient dosages.

Patients were visited for six consecutive months and clinical information regarding the type and number of the seizures and side effects of the drug were recorded through interviewing their parents.

At the end of the period, an electroencephalography (EEG) was done and ZNS efficacy and safety was evaluated. Seizure frequency in a week was compared to that of three months before and six months after ZNS use and the following classification was done on this basis:

1. Seizure free: all the seizures stopped
2. Improved: more than 50 % reduction in seizure frequency
3. Unchanged: no notable change was seen in seizure frequency
4. Worsened: seizure frequency increased more than 25%

It was impossible to check the serum level of Zonisamide in our center or any other center in Yazd.

Chi-square or Fisher exact test were used for data analysis of qualitative variables and mean values were compared using T-test. Differences were considered significant at P values of less than 0.05.

This study was approved by the Ethics Committee of Shaheed Sadoughi University of Medical Sciences, Yazd, Iran.

Results

The efficacy of ZNS was evaluated in 40 children with LGS and intractable seizures. Twenty one boys (52.5%) and 19 girls (47.5%) with a mean age of 6.6 ± 3.6 years (range = 1.5 -14 year) were included in this study.

Onset age of seizures was one month to 3 years (mean ± SD: 9.96 ± 8.16 month).

From the viewpoint of major seizure types, 14 children (35%) showed mixed type (more than one type of seizure), eight (20%) had generalized tonic-clonic (GTC), eight (20%) had myoclonic, six (15%) had tonic and four (10%) had atonic seizures.

Seizures were not controlled despite the usage of 4-15 (mean ± SD: 8. 6 ± 2.8) antiepileptic drugs.

On the basis of etiologic classification, we noted symptomatic LGS in 31 (77.5%) and idiopathic LGS in 9 (22.5%) patients. The etiology in the symptomatic group was structural CNS dysgenesia in 9, inborn errors of metabolism in 9, chromosomal abnormality and genetic syndromes in 4, hypoxic ischemic encephalopathy in 4, tuberous sclerosis in 3 and congenital infection in 2 children.

Brain MRI was normal in 19 (47%) children. At the end of six months of ZNS treatment, 25% (N=10) of the patients became seizure free and 25% (N=10) had more than 50 % reduction in seizure frequency while 35% (N=14) had no notable change in the frequency of seizures and seizure frequency increased> 25 % in six children.

The mean dose of ZNS for seizure control was 11. 8 ± 2.8 mg/kg/day (range: 4-16).

Results of efficacy analysis based on seizure type are shown in Table 1, indicating a good response to ZNS (all seizures stopped or more than 50 % reduction in seizure frequency) in 62.5 % of the myoclonic and GTC seizures, 50% of the atonic and 33.4 % of tonic seizures. Efficacy of the drug was not significantly different in different seizure types.

For statistical analysis with Chi-square test GTCS, myoclonic, tonic and atonic seizures were considered as generalized seizures. Table 2 shows the frequency distribution of good response based on some clinical and paraclinical characteristics of patients, indicating that the drug has been more effective in girls and patients without drug side effects.

Table 3 shows the comparison between mean age, age at seizure onset and seizure frequency three months before and six months after treatment based on etiologic classification, indicating that symptomatic LGS was more in younger patients and that before and after treatment, seizure frequency was more in the symptomatic group.

Transient and mild side effects were seen in 25% (N=10) of patients consisting of drowsiness in 10% (N=4), hyperthermia in 5 % (N=2) and irritability, fatigue, ataxia and anorexia, each in 2.5% (N= 1). All adverse effects occurred in the first or second week of the titration phase and disappeared in one or two weeks. No serious adverse events such as idiosyncratic skin reactions, metabolic acidosis or pancreatitis were seen.

Discussion

Management of LGS depends on the response of the patients and we are often forced to use two or more types of AEDs in combination. It is difficult to provide recommendations for the treatment of LGS in the absence of comparative trials. Therefore, AEDs with better efficacy and fewer side effects are fiercely needed. In this report, the efficacy and safety of Zonisamide in

children with LGS was evaluated.

In the present study, ZNS treatment controlled all seizures in 25% of the patients. However, this rate varies between 4.8 % and 67% In other studies (8,11-13, 17-20).

In this study, more than 50% reduction in seizure frequency was seen in 25% of the patients which is consistent with another study [29% (17)] while this rate varies between 22 % and 75.4% in other studies (8,11-13, 17-24).

Possible explanations for this variety are ethnical and geographic differences, duration of follow-up, sample size, pharmacokinetic aspects, methods of patient selection, age range of the patient, etc.

In our study, the drug was effective in 62.5% of the GTC and myoclonic seizures. In a study by Yamauchi, 58% of the patients with generalized seizures and 50% of the patients with myoclonic seizures showed improvement with Zonisamide treatment (25). In another study, 51.2% of the patients with generalized seizures and 55.6% of the patients who had myoclonic seizures showed a greater than 50% reduction in the frequency of seizures (8).

We noted that ZNS was more effective in generalized seizures in comparison with mixed seizures. In a study by Park et al, evaluation of the efficacy and safety of ZNS monotherapy in epileptic patients showed that generalized seizures and partial seizures with or without secondary generalization were well controlled (19).

We also found that the mean dosage of ZNS for seizure control was 11.6 mg/Kg/day which is higher than other studies [5.7 (12), 7.7 (23), 8.2 (8), and 9.1 (20)]. Differences in race or drug pharmacokinetics may be responsible.

In the present study, the drug was more effective in girls. One possible explanation for this discrepancy is that seizure onset is later and idiopathic LGS is more frequent in girls. However, other researches with longer follow-up periods and bigger sample sizes are required to answer this difference.

In our study, ZNS adverse effects were seen in 25% of the children. Other studies, however, have reported rates between 4-80% (8,11-14,17-23,26). We also noted that the most common side effect, as also reported by other reports, was drowsiness (8,11,13, 22).

The most common side effects that are documented in other studies include weight loss [13% (18) and 4.5% (17)], irritability and a reduced appetite (12), mental-psychiatric symptoms in 19.4% and gastrointestinal symptoms in 8.7% (26), decreased appetite, somnolence, and asthenia (22), memory loss in 35%, attention deficit in 27% and weight loss in 20% (19). Differences in race, age of the patients or drug pharmacokinetics may be responsible.

In conclusion, ZNS could be considered as an add-on therapy in the management of intractable epilepsy in LGS.

Table 1: Efficacy results of Zonisamide after six months based on seizure type

Response / Seizure type	Seizure free		Improved		Unchanged		Worsened		Total
	Number	Percent	Number	percent	Number	Percent	Number	Percent	
Mixed	3	21.5	3	21.5	5	35.5	3	21.5	14
GTC	3	37.5	2	25	2	25	1	12.5	8
Myoclonic	2	25	3	37.5	2	25	1	12.5	8
Tonic	1	16.7	1	16.7	3	49.9	1	16.7	6
Atonic	1	25	1	25	2	50	0	0	4
P. value	0.96								

Table 2: Frequency distribution of the good response based on some clinical and paraclinical characteristics of the patients

Data \ Good response		Yes		No		P. value
		Number	Percent	Number	Percent	
Sex	Female	13	68.4	6	31.6	0.03
	Male	7	33.3	14	66.7	
Seizure type	Mixed	6	43	8	57	0.5
	Generalized	14	54	12	46	
Etiologic class	Symptomatic	14	45	17	55	0.26
	Cryptogenic	6	66.7	3	33.3	
Family history of epilepsy	Yes	6	75	2	25	0.11
	No	14	44	18	56	
Brain MRI results	Abnormal	8	38	13	62	0.16
	Normal	12	63	7	37	
Slow spike wave pattern in six months after treatment EEG	Yes	3	37.5	5	62.5	0.43
	No	17	53	15	47	
Occurrence of ZNS side effects	Yes	2	20	8	80	0.03
	No	18	60	12	40	

Table 3: Comparison of mean age, age at seizure onset and before and after seizure frequency based on the etiologic class

Data \ Groups	Symptomatic Mean ± SD	Idiopathic Mean ± SD	P.value
Age (in years)	5.97 ± 3.38	8.8 ± 3. 6	0.03
Age at seizure onset (in months)	9.01 ± 6.59	13.17 ± 12.03	0.18
Seizure frequency before treatment (in weeks)	16.77 ± 15.65	2.72 ± 1.39	0.01
Seizure frequency after treatment (in weeks)	14.84 ± 2.98	2.03 ± 1.69	0.04

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