RESEARCH ARTICLE

EFFICACY AND SAFETY OF LAMOTRIGINE IN LENNOX-GASTAUT SYNDROME

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Abstract

Objective

The Lennox-Gastaut syndrome (LGS), one of the most difficult epilepsy syndromes to treat, is characterized by a triad of intractable seizures of various types, a slow (< 2.5-hertz) spike-wave pattern in EEG and mental retardation. The aim of this study was to evaluate the efficacy and safety of lamotrigine as add-on therapy in intractable epilepsy of children with LGS.

Materials & Methods

In a quasi- experimental study, 40 children with LGS referred to the pediatric neurology clinic of Shaheed Sadoughi Hospital in Yazd, between August 2007 and to November 2008, were evaluated.

Results

Twenty-two boys and 18 girls with a mean age of 4.12 ± 1.8 years were evaluated. At the end of three months of treatment with lamotrigine, 12% were seizure free, 52% had> 50% reduction in seizure frequency and 12% had increase in seizures. Means of seizure frequency/per week, before and after treatment were 70 (range 1-180) and 18.6 (range 0-60) respectively, indicating effectiveness of the drug in seizure reduction (P value = 0.003). The drug was effective in 72 % of mixed type seizures, 40% of generalized tonic-clonic and 33% of drop attack and tonic seizures. Transient side effects were seen in 12.5% (drowsiness in 3 and ataxia in 2 children). No serious side effects were seen.

Conclusion

Lamotrigine should be considered as an add-on therapy in management of intractable epilepsy in LGS.

Keywords: Lennox-Gastaut syndrome (LGS), Lamotrigine, 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, followed by Lennox and Davis' report of the symptomatic triad of the syndrome. Later, Gastaut expanded on the original observations of Lennox and Davis" (1). This syndrome is characterized by the triad of intractable seizures of various types, particularly tonic and atonic seizures; it also includes absence and myoclonic seizures (atypical petit mal) as well as nonconvulsive status epilepticus, a slow (less than 2.5-hertz) spike-wave pattern on the interictal EEG that is generalized and of highest voltage in the frontal region (also called an atypical spike and wave pattern) and mental retardation (occasionally progressive) with or without other neurologic

abnormalities (2).

LGS accounts for 3-10 percent of all cases of childhood epilepsy but it is a major contributor to morbidity and seizures that are often associated with falls and injuries (3). Although seizure onset varies from 6 months to 16 years, in two-thirds of cases, the onset occurs between 2 and 14 years of age (4).

Etiologic classification of LGS

1. Primary or idiopathic
2. Secondary or symptomatic:

- Prenatal: Cerebral dysgenesis, tuberous sclerosis, congenital infections, stroke
- Perinatal: Hypoxia/ischemia, intracranial hemorrhage
- Postnatal: CNS infections, Postinfectious process, Hypoxia/ischemia, cerebral vascular disease, head injury, hypoglycemia, and degenerative disorders (5).

In approximately 40% of affected children, a known cause cannot be identified, although increasingly, these children are found to have genetic disorders, particularly chromosomal syndromes (6). Symptomatic LGS has worse prognosis than cryptogenic etiology (7). Medical management of LGS is often difficult and seizures are mainly drug resistant. Complete recovery, seizure-free with normal development is very unusual in LGS. The optimal therapy is uncertain and may depend in part upon the underlying etiology. Main treatment is based on antiepileptic drugs (AEDs) and some children may need more than one mode of treatment (8). Other methods for treatments of refractory seizures include the ketogenic diet and surgical options, which include vagus nerve stimulation, corpus callosotomy, stereotactic surgical implantation of electrodes to the centromedian nuclei of the thalamus, etc (6,8, 9).

Different drugs are used as the first-line agents in LGS treatment such as valproate (10), zonisamide, topiramate (11) and clonazepam (12).

Other antiepileptic drugs such as lamotrigine(1,6,8,13-16), felbamate (6,8,14,16), benzodiazepines and phenobarbiturates(1,8) and prednisone (17) have been used in LGS. On the other hand, carbamazepine can precipitate drop attacks in some of these children. No single treatment regimen could be considered superior to others, and no study to date has shown any one drug to be highly efficacious (6). It is difficult to provide recommendations for the treatment of LGS in the absence of comparative trials. Therefore, AEDs with greater efficacy and fewer side effects are urgently needed. Management depends on the response of patients and we are often forced to use two or more kinds of AEDs in combination.

Lamotrigine (LTG), initially approved in 1994 for the adjunctive treatment of generalized seizures of LGS in children aged over 2 years (13), is one of new antiepileptic which acts as voltage-sensitive sodium channel to stabilize neuronal membranes and presynaptic inhibition of excessive release of excitatory amino acids, particularly glutamate and aspartate. LTG suppresses postsynaptic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors and reduces glutamate release in granule cells of dentate gyrus. The postsynaptic effect can also be one of the underlying mechanisms of LTG (18).

Guidelines issued by the American Academy of Neurology (AAN) state that LTG can be used as initial therapy in patients with newly diagnosed partial epilepsy and idiopathic generalized epilepsy, as well as mixed seizure disorders (19).

The purpose of this study was to evaluated the efficacy and safety of LTG in all types of seizures among children with LGS in Yazd, Iran.

Materials & Methods

This quasi- experimental (before and after) study was conducted on children with LGS and refractory epilepsy referred to pediatric neurology clinic of Shaheed Sadoughi Medical Sciences university from August 2007 to November 2008 in Yazd, Iran.

The diagnostic criteria for the LGS in this study were based on the International League Against Epilepsy (ILAE) classification (20,21). In fact the patients were considered as the control group (before) and the case group (after) LTG treatment. Care was taken to include LGS patients aged 1-18 years, having had at least one seizure/week, not responding to an adequate dosage of at least two conventional AEDS (in single or combination), and last not having used LTG before.

Information collected at baseline included demographic data and epilepsy characteristics such as etiology, age of onset, type and frequency of seizures and AEDS

history. Results of physical and neurologic examination, laboratory analysis, EEG and brain CT scan or MRI were included. Laboratory blood analysis, both at the initiation of the study and three months after treatment included assessment of calcium, urea, creatinine, alanine aminotransferase, aspartate aminotransferase and complete blood count.

The trial had three phases as given

1. Baseline phase : Seizure frequency was recorded for a period of 3 months before adding LTG.
2. Titration phase: To minimize side effects of the drug, LTG was added to the previous AEDS regimen in a 4 week period as follows: 1, 2, 3, 5 mg / kg / day in patients who had taken valproic acid simultaneously, and 3, 5, 7, 10 mg / kg / day in those without valproic acid usage
3. Maintenance phase: Maximum dose or that which controlled seizures was continued for 3 months. No new AEDS were added to LTG and concomitant drugs, but the dose of the concomitant could be increased or decreased. Patients were visited for three consecutive months to document clinical information related to their parents, the types and numbers of seizures, drug side-effects and paraclinical investigations. At the end of the period, LTG efficacy and safety were evaluated. Seizure frequency/ month was compared to that of 3 months before and after LTG use and was used the following classification:

1. Seizure free: Total cessation of seizures
2. Improved: Over 50 % reduction in seizure frequency
3. Unchanged: No notable change witnessed in seizure frequency
4. Worsened: Over 25% increase in seizure frequency

We compared means of seizure frequency before and after treatment using the paired-samples t-test. X^2 analysis was used for data analysis of qualitative variables and differences were considered significant at $P<0.05$.

This study has been approved by the ethics committee of the Shaheed Sadoughi University of Medical Sciences, Yazd, Iran.

Results

LTG efficacy was evaluated in intractable seizures of 45 children with LGS. Three patients were excluded for poor compliance. Coetaneous drug rash was seen in 2 of the patients, one or two weeks after LTG consumption that resolved with discontinuation of LTG and there was no need for hospitalization; these two patients were excluded from the study but included only in safety analysis. Eventually 22 boys (55%) and 18 girls (45%) with a mean age of 4.5 ± 2.9 years (range 1-14 yr) were evaluated.

Age of onset for seizures ranged between 7 months to 2 years (mean 0. 9 yr). From the viewpoint of major seizure types, 29 children (72.5 %) showed mixed type (more than of one type of seizure), five (12.5 %) generalized tonic-clonic seizure (GTCS), three (7.5 %) drop attack and three tonic (7.5%).

Seizures were not controlled despite usage of 4 -12 (mean= 6.4) antiepileptic drugs.

Based on the etiologic classification of LGS, 22 (55%) were symptomatic and 18 (45 %) were idiopathic. Neuroimaging results were normal in 24 (60 %) of children.

Results of the efficacy analysis are shown in table 1, which indicates good response to lamotrigine, with either complete cessation of seizures, or >50% reduction in seizure frequency being observed in 64% of patients. Mean of seizure frequency/week, before and after treatment were 70(range1-180) and 18.6(range0-60) respectively, demonstrating the efficacy of LTG. (Confidence interval 95%, t =3.5, p value 0.003)

Good responses were seen in 72% (21/29) of mixed type, 40% (2/5) of GTCS, 33% (1/3) of drop attack and in 33% (1/3) of tonic seizures. For statistical analysis, GTCS, drop attack and tonic seizures were considered as generalized seizures.

Table 2 shows effectiveness of LTG on seizure types and etiologic classes of LGS and indicates that drug efficacy did not differ in types of seizure and in etiologic classes of LGS.

The mean dosage of LTG for seizure control was 8.7 mg/Kg/day (range: 3-10). Transient and mild side effects were seen in 12.5% (N=5) of patients; drowsiness in 7.5% (n=3) and ataxia in 5% (n=2), all of which disappeared in one or two weeks. No serious adverse events such as hematologic abnormality, hepatotoxicity or nephrotoxicity were observed.

Table 1. Efficacy results of lamotrigine after three months

Percent	Number	Efficacy result
12	5	Seizure free
52	21	> 50% reduction of seizure frequency
23	9	No notable change witnessed in seizure frequency
12	5	Worsened (seizure frequency increased > 25 %)
100	40	Total

Table 2. Effectiveness of LTG on seizure types, etiologic classification

Data		Good response		Not response		P-value
		Number	Percent	Number	Percent	
Seizure types	Generalized	5	45	6	55	0.11
	Mixed	21	72	8	28	
LGS etiologic classification	Symptomatic	12	55	10	45	0.436
	Idiopathic	12	67	6	33	

Discussion

Lamotrigine efficacy and safety in seizures of children with LGS were evaluated in the current study and a good response to LTG was seen in 64 % of patients with Lennox-Gastaut syndrome, findings consistent with 60 % result of two other studies (22,23); however in other studies, this rate varied between 33 % and 91% (22-25), which may be explained by ethnical and geographic differences, duration of follow up, pharmacokinetic aspects, methods of patients selection, etc.

According to the results of the study, lamotrigine was a useful add-on therapy in treating epilepsy in children with LGS, findings in agreement with those of several other studies (14,15,22, 25); in a study from Taiwan, LTG was found to have excellent response in patients after ineffective callosotomy (26).

In this study, the drug was effective in 40 % of patients with GTCS. In Motte et al study, over 50 % reduction in seizure frequency was seen in 43 % of GTCS of LGS children (25). In another study 72% of patients aged 2-55 years with primary GTCS experienced a ≥ 50% reduction in frequency of seizures (27).

In this study, erythematous skin rash was seen in 5 % (2/42) of patients but in other studies, this rate varied between 3-17% (11,22,28,29) The frequency of rash increases with more rapid titration and concomitant valproate; hence it is recommended to start LTG with low dose and slow titration. However, none of our patients had concomitant valproate or high drug dose, and skin rash was seen in them in the first or second week of treatment, which could be due to differences in race or drug pharmacokinetics.

In the present study, the most common side effect was drowsiness, a finding similar to those of other studies (27,30,31). Headache was not seen in any of our patients, but was a common side effect documented in

other studies (30-33).

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