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Original Article

Efficacy and safety of lamotrigine in refractory epilepsy of children

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Abstract. It is known that current antiepileptic drugs can not control seizures in 20-30% of patients. The aim of this study was to evaluate the efficacy and safety of lamotrigine as add-on therapy in intractable epileptic children in Yazd- Iran. In a drug study, 42 children with mean age of 5/35 ± 4 years, 23 boys and 19 girls with refractory seizures and seeking treatment, recruited to be subjects of this study. Mixed and myoclonic were the most common seizure types (38% and 31% respectively). At the end of three months of lamotrigine treatment concomitantly with previous AED, 31% became seizure free, 35.7% had more than 50% reduction in seizure frequency and 12% had increasing seizures. All of seizures in absence and juvenile myoclonic epilepsies stopped with lamotrigine. Good drug response (stopping of seizures or > 50% of reduction in seizure frequency) was seen in 100% of idiopathic, 67% of cryptogenic and 54% of symptomatic epilepsies. 75% of Lennox-Gastaut syndrome and progressive myoclonic epilepsy and 33% of West syndrome had good response. Drug rash was seen in 6.7% of children and serious hematologic abnormality, hepatotoxicity and nephrotoxicity side effects were not seen. Lamotrigine can be considered as an effective and safe drug in controlling of intractable epilepsy of children especially in absence and juvenile myoclonic epilepsy.

Key words: Refractory epilepsy, lamotrigine, add-on therapy, children

1. Introduction

Epilepsy is one of prevalent pediatric neurological problems with annual prevalence of 0.5-0.8% (1). Intractable or refractory epilepsy includes 20-30% of epilepsies in which two of first line antiepileptic drugs (AEDs) with sufficient dose is taken, even though the patients might, at least, have one seizure monthly (2). Therefore, effective control of seizures is necessary to reduce epilepsy related morbidity and mortality and new AEDs with greater efficacy and fewer side effects are fiercely needed.

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Lamotrigine is one such agent and the drug acts as a voltage- sensitive sodium channel to stabilize neuronal membranes and presynaptic inhibition of excessive release of excitatory amino acids, particularly glutamate and aspartate (1). Lamotrigine suppresses postsynaptic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors and reduces glutamate release in granule cells of dentate gyrus. So, postsynaptic effect can be one of the underlying mechanisms of the drug [(3)].

Studies have shown the effectiveness of lamotrigine in partial, absence, myoclonic and generalized seizures as in West, Lennox-Gastaut, Rett and Angelman syndromes (4-17).

Guidelines issued by the American Academy of Neurology (AAN) state that lamotrigine can be used as an initial therapy in patients with newly diagnosed partial epilepsy and idiopathic generalized epilepsy, as well as mixed seizure disorders (18) .

The purpose of this study was to evaluate the efficacy and safety of lamotrigine in children

Table 1.Clinical characteristics of the patients

Sex (45%)	Male = 23 (55%)	Female=19
Seizure frequency (per month)	Range=1-750	Mean=101
After treatment seizure frequency (per month)	Range=0-240	Mean=41.5
Onset age of seizures	Range = 3 days -14 yr	Mean = 1.47 yr
Number of past AEDs	Range = 2-12	Mean= 5.6
Number of concomitant AEDs	Range=1-3	Mean=1.57

Table 2. Results of neuroimaging of patients

Result	n
Normal brain CT scan	29
Focal brain encephalomalacia	3
Brain atrophy	6
Periventricular leukomalacia (with MRI)	5
Calcified tubers of tuberous sclerosis in CT scan	2
Uncalcified tubers of tuberous sclerosis in MRI	1
Hydrocephaly and diffuse brain calcifications	1
Leukodystrophy (with MRI)	1
Cerebral and cerebellar atrophy and corpus callosum agenesis	1

Table 3. Results of efficacy of lamotrigine after 3 months

Efficacy result	n (%)
Seizure free : all the seizure stopped	13 (31)
Improved : more than 50% reduction of seizure frequency	15 (35.7)
Unchanged : no notable change witnessed in seizure frequency	9 (21.4)
Worsened (seizure frequency increased > 25 %)	5 (11.9)

with intractable epilepsy in Yazd, central city of Iran.

2. Materials and methods

As the patients had seizure, we did not ethically permit ourselves to use placebo and in fact, we were coerced to compare patients' conditions before and after the study.

This drug study was conducted on 47 patients with refractory epilepsy, referred to pediatric neurology clinic of Shaheed Sadoughi Medical Sciences University from November 2007 to August 2008 in Yazd, Iran. Patients were considered as control group before, and case group after lamotrigine treatment. Care was taken to include patients aged 1-18 years, not responded to an adequate dosage of at least two conventional AEDs in single or combination, had at least one seizure in a month and finally not used lamotrigine formerly.

Information collected at baseline included demographic data and epilepsy characteristics such as etiology, age of onset, type and frequency of seizures (based on clinical descriptions by parents) and AEDs history. Results of physical and neurologic examination, laboratory analysis, EEG and brain CT scan or MRI, were included. Laboratory blood analysis consisted of calcium, urea, creatinine, alanine aminotransferase, aspartate aminotransferase and complete blood count done at the beginning of the study and after three months of treatment. The trial had three phases as bellows:

1. Baseline phase: Seizure frequency was recorded for a period of 3 months before adding lamotrigine .

2. Titration phase: To minimize side effects of the drug , lamotrigine was added to the previous AEDs regimen in a 4 week period for 1 , 2 , 3 , 5 mg/kg/day in patients who had taken valproic acid simultaneously , and for 3,5,7,10 mg/kg/ day in those without valproic acid usage .

3. Maintainance phase : Maximum dose or the one which controlled seizures, continued for 3 months. For better evaluation of only lamotrigine effect, no new AEDs added to concomitant drugs, but the dose of the concomitant could be increased or decreased. Patients were visited for three consecutive months, and clinical information of their parents about the type and number of seizures, side effects of the drug and paraclinical investigations of them, were recorded. At the end of the period, lamotrigine efficacy and safety (via filling of questionnaire by patients or their parents and assessment of laboratory data) were evaluated. Seizure frequency in a month was compared to that of three months before and after lamotrigine use, and the following classification was done on this basis:

1. Seizure free: all the seizures stopped.

2. Improved: more than 50% of reduction in seizure frequency

3. Unchanged: no notable change witnessed in seizure frequency

4. Worsened: seizure frequency increased more than 25%.

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

Informed consent was taken from patients' parents and this study has been approved by the ethic committee of Shaheed Sadoughi University of Medical Sciences, Yazd, Iran.

Meanwhile, the researchers got no support from the drug company.

3. Results

The lamotrigine efficacy was evaluated in 47 epileptic children. Two patients were excluded for poor compliance (consumption of insufficient drug dosage or discontinued usage by parents). Cutaneous drug rash was seen in 3 of the patients in the first or second week after lamotrigine consumption, which resolved with discontinuation of lamotrigine and no need to hospitalization and because they did not receive full dose of the drug and not complete therapeutical program, were excluded from the study and included only in the safety analysis. Finally 42 children from 1 – 15 years with mean age of 5/35±4 years were evaluated. Clinical and paraclinical characteristics of patients are presented in Table I. 24% (10/42), 81% (34/42) and 90% (38/42) had positive family history of epilepsy, neurodevelopmental delay and abnormal EEG , respectively.

From viewpoint of seizure type, 16 children (38%) showed mixed type (more than one type of seizure), 13 (31%) myoclonic, 5 (12%) generalized tonic-clonic, four focal (9.5%), three (7%) generalized tonic, and finally one (2.5%) abscense. On the basis of seizure etiologic classification, we witnessed symptomatic epilepsy in 22 (52.4%), cryptogenic epilepsy in 12 (28.6%) and idiopathic epilepsy in 8 (19%). Results of neuroimaging are shown in Table.II . Brain CT scan was done in all of the patients which was normal in 69% (29/42). Brain MRI was done in 23 children (55%) as well, which detected periventricular leukomalacia in five, uncalcified tubers of tuberous sclerosis in one, and leukodystrophy in one patient with normal CT scan .

Results of efficacy analysis are shown in Table.III which indicate good response to lamotrigine (all the seizures stopped or > 50 % of reduction in seizure frequency) were seen in 67% of patients . Statistical analysis revealed the efficacy of lamotrigine. (Confidence interval =95%, t =3.16 and p value = 0.003) Number of concomitant AEDS was one, two and three in 22 , 16 and 4 patients, respectively. Best response was seen in the combination of sodium valproate and lamotrigine which stopped seizures in 67% (4 of 6 patients) of them. Table IV shows response to lamotrigine based on some factors which indicate, birth asphyxia, hypoxic – ischemic encephalopathy and neurodevelopmental delay are associated with unfavorable outcomes.

Mean dosage of lamotrigine for seizure control was 7.6 mg/Kg/day but lowest and highest dosages for stopping of seizures were 5 mg/kg/day and 10 mg/kg/day, respectively. Concomitant AEDs are shown in Table.V. Table.VI shows effectiveness of lamotrigine on all seizure types, etiologic classes and epileptic syndromes. The best outcome was seen in absence seizure all of whom became seizure free. Good response was seen in 81% (13/16) of mixed type, 75% (3/4) of partial, 67% (2/3) of generalized tonic, 60% (3/5) of

Table 4. Lamotrigine response based on some factors

Factor		Good response	No response	p value
Birth asphyxia	Yes	4	8	0.004
	No	24	6	
Family history of epilepsy	Yes	9	1	0.271
	No	19	13	
Developmental delay	Yes	20	14	0.02
	No	8	0	
EEG results	Normal	2	2	0.59
	Nonspecific abnormal	14	5	
	Epileptic abnormality	12	7	

generalized tonic clonic and 46% (6/13) of myoclonic seizures.

Table 5. The concomitant antiepileptic drugs with lamotrigine

Phenobarbital	18
Clobazam	12
Primidone	8
Valproate	5
Clonazepam	5
Nitrazepam	5
Vigabatrin	5
Carbamazepine	4
Phenytoin	3

*Patients may have been taking 1-3 concurrent AEDs.

Transient and mild side effects were seen in 22% (n=10) of patients consisting of drowsiness in 15% (n=7) , ataxia in 4% (n=2) and diplopia in 2% (n=1), all of which disappeared in a few days. Fortunately, no serious adverse events such as hematologic abnormality, hepatotoxicity and nephrotoxicity were seen.

4. Discussion

The purpose of this study was to evaluate efficacy and safety of lamotrigine use in intractable epileptic children in Yazd- Iran.

In the present study, good response to lamotrigine was seen in 67% of patients but in other studies, this rate varied between 30% and 90% (7,9,11,14,19). To compare the effectiveness of the drug in other studies in middle Eastern community of seizure patients , lamotrigine was effective in 52.5% of patients in another Iranian research in Mofid Children Hospital in Tehran-Iran (11). The drug reduced seizure frequency by at least 50% in 57.1% of patients with partial seizures and in 53.6% of patients with primary generalized seizures in Turkish children with refractory epilepsy (20) and in Israel, 66% of women with Catamenial epilepsy (epileptic seizures in the female occurring rhythmatically with the menstrual cycle) had reduction > 50% in the number of seizures (21). In Taiwan, 43.5% had a > 50% reduction in seizure frequency (22). In other studies in Western and other countries, lamotrigine was effective in 53% (4) , 42% (5) and 71% (11) in the USA , 77% (8) in Spain , 59% in Bosnia (23), 47% in Netherlands (24) and in 94% of women with epilepsy in Berlin ,Germany (25). Possible explanations for this variety are: ethnical and geographic differences, sex, age group and methods of patients selection and so on. According to the results of the study, lamotrigine was effective in all types of seizures which are in agreement with other studies (9,11, 14,19).

In this study, the best results were obtained in patients with absence and juvenile myoclonic epilepsy, all of whom became seizure free. However, the number of our cases is too small to discuss about lamotrigine effect on such seizures, other studies recommend that lamotrigine is one of first-line options for absence and juvenile myoclonic epilepsy. In juvenile myoclonic epilepsy of adolescent females, lamotrigine was treatment of choice (13, 26). In present study, the drug was effective in 75 % of partial seizures while in that of Piña-Garza et al, in randomized, double-blind, placebo-controlled trial to assess the efficacy and tolerability of adjunctive lamotrigine for the treatment of partial seizures in infants aged 1 to 24 months, 53% of patients had a≥50% reduction in frequency of partial seizures with

Table 6. Effectiveness of lamotrigine on seizure types , etiologic classification and epileptic syndromes

Data	Good response	Not response	
	n (%)	n (%)	p - value
Seizure types			
Generalized	12 (54)	10 (46)	
Partial	3 (75)	1 (25)	0.03
Mixed	13 (81)	3 (19)	
Seizure etiologic classification			
Symptomatic	12 (54)	10 (46)	
Idiopathic	8 (100)	0 (0)	0.024
cryptogenic	8 (67)	4 (33)	
Epileptic syndromes			
Lennox- Gaustat syndrome	12 (75)	4 (25)	
Progressive myoclonic epilepsy	6 (75)	2 (25)	0.017
Juvenile myoclonic epilepsy	2 (100)	0 (0)	
West syndrome	3 (33)	6 (67)	
Not definite syndromes	5 (75)	2 (25)	

lamotrigine (4) and in Naritoku et al study to evaluate the efficacy and tolerability of once-daily adjunctive lamotrigine extended-release for partial seizures in patients more than 12 years old, diagnosed with epilepsy with partial seizures , 42% had a ≥ 50% reduction in frequency (5).

Therefore lamotrigine is an effective drug in the treatment of partial seizures. In this study, the drug stopped seizures in 40 % of patients with generalized tonic clonic seizure which is similar to USA study (48%) (14) and according to the results of the present study, lamotrigine was effective in 80 % of generalized tonic clonic seizures. In another study 72% of patients aged 2 to 55 years with primary generalized tonic-clonic seizures experienced a≥50% reduction in frequency of seizures (27).

In present study, good response to lamotrigine was seen in 75% of patients with Lennox-Gastaut syndrome but in other studies, this rate varied between 33% and 91% (11,28,29).

In this study, erythematous skin rash was seen in 6.7% (3/45) of patients which is consistent with another study (7%) (13), even if up to 17 % was also reported (30). The frequency of rash increases with more rapid titration and concomitant valproate so, it is recommended to start lamotrigine with low dose and slow titration. However, none of our patients had concomitant valproate or high drug use, skin rash was seen in them in the first or second week of treatment. Differences in race or drug pharmacokinetic may be responsible.

In present study, the most common side effect was drowsiness which is similar to other studies. (5,8,27,31) headache was not seen in any of our patients, but in other studies, it was the most common side effect (5,8,9,31).

5. Conclusions

This study supports efficacy and safety of lamotrigine in controlling of intractable epilepsy in children and indicates the drug should be considered as an add-on therapy in the management of refractory epileptic syndromes.

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