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LAMOTRIGINE AS ADD-ON THERAPY IN CHILDREN WITH DRUG-RESISTANT EPILEPSY (IRANIAN EXPERIENCE)

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ABSTRACT

Lamotrigine (LTG), a newly developed antiepileptic drug (AED), is efficacious in treating refractory epilepsy. This study was designed to evaluate the efficacy and safety of LTG as add-on therapy in 40 children with refractory epilepsy.

The trial was an open-labeled prospective study in children with drug-resistant epilepsy aged <14 years, who had at least 4 seizures per month in spite of receiving at least 3 AED's. Initial LTG dose and titration was adjusted based upon the AED's which were taken simultaneously.

Lamotrigine was increased in steps to maximal dose within 4 weeks and maintained for 3 months while pre-existing AED's remained unchanged. Overall efficacy was defined if >50% reduction of seizure frequency was achieved during 3 months follow up. Hematological and biochemical parameters were checked before and after the trial in all patients. The evaluation of drug safety consisted of chart review for treatment-emergent adverse events.

Among 40 patients who completed the trial, 21 of them (52.5%) had >50% reduction in seizure frequency. Lamotrigine was effective in all seizure types, particularly typical absence. Lennox-Gastaut syndrome also responded well. Skin rashes occured in 5 patients (10.6%) and resulted in LTG discontinuation. No significant changes were noted in laboratory results.

These results indicated that LTG is well tolerated and is effective in controlling a variety of seizure types, especially absence epilepsy.

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INTRODUCTION

The inability of current AED's to control seizures in about 20-30 % of patients with epilepsy,[1] emphasizes the urgent need for efforts to develop new anti-epileptic drugs. Lamotrigine (LTG) is a recently developed AED that acts primarily by blocking voltage-dependent sodium channels to stabilize the neuronal membrane and inhibit the release of excitatory neurotransmitters, principally glutamate.

It has been proven to be effective as add-on treatment in adults with refractory partial and secondary generalized tonic-clonic seizures.[3,4] In addition, LTG has demonstrated its efficacy in pediatric patients with drug-resistant epilepsies including partial, myoclonic, absence,

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tonic, atonic seizures and Lennox-Gastaut syndrome (LGS).[5-10]

By the best of our knowledge, this is the first systematic and prospective study that reports the efficacy and safety of LTG as add-on therapy in childhood refractory epilepsy in Iran.

PATIENTS AND METHODS

Patients were enrolled in this study at Mofid Children's Hospital in Tehran, Iran, between September 1997 and February1998. Eligible patients consisted of children with refractory epilepsy who had a minimum seizure frequency of four per month and did not respond to an adequate dosage of at least 3 AED's in single or in combination.

Patients who had progressive neurologic disorders were excluded. All patients were classified according to the recommendation of the commission on the classification and terminology of the International League Against Epilepsy (ILAE), 1989.[11] For each patient the predominant seizure type was determined according to its frequency and /or severity. In LGS patients who were diagnosed with atonic, tonic and myoclonic seizures that resulted in falls were considered drop attacks for purposes of data collection and analysis. Information collected at baseline included demographic data and epilepsy characteristics: etiology, age of onset, type and frequency of seizures, AED history, results of physical and neurologic examination, laboratory analysis (hematology and biochemistry), electroencephalography (EEG) and brain computed tomography (CT) were included.

The trial consisted of three phases:

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

2.Titration phase: LTG was added to the previous AED's regimen according to the following schedule: for patients who were already on valproate the starting dose was 1 mg /kg /day whereas it was 2mg /kg /day in patients treated with other AED's. The amount of LTG was gradually increased to the maximum dose within 4 weeks (Table I).

Table I. Lamotrigine titration according to concomitant AED.

Week	Valproate	Other AEDs
1	1mg/kg/day	2 mg/kg/day
2	2mg/kg/day	5 mg/kg/day
3	3mg/kg/day	8-10 mg/kg/day
4	4-6mg/kg/day	12-15 mg/kg/day

3. Fixed LTG dose schedule period: Patients were observed prospectively at monthly intervals for 3 months. Parents were instructed to record the type and number of seizures in the patient diary. During this period clinical and neurologic examinations were performed monthly, along with paraclinical investigations. In order to avoid adverse events due to pharmacokinetic interactions, the dosage of concomitant AED's were kept unchanged. The frequency of seizures in the LTG treatment period was compared with baseline data. Efficacy was evaluated monthly. Improvement was defined as a decrease in seizure frequency of >50%, worsening was determined if an increase in seizure frequency of >25% happened, patients with results between these two limits were considered unchanged.

Safety assessment: Adverse events were documented by means of interviews, clinical and laboratory examinations monthly.

Informed consent was obtained before entry to the study.

RESULTS

Forty-seven patients presenting with refractory seizures were enrolled. The clinical characteristics at baseline are summarized in Table II.

Although the subjects were required to have a minimum of 4 seizures per month to be eligible, the average seizure frequency at baseline was much higher (multiple daily or weekly seizures). All patients were resistant to 4-12 AEDs (mean 6.7 drugs per patient) including phenobarbital, primidone, phenytoin, carbamazepine, so-

Table II. Characteristics of the patients included in the trial.

Sex	Male = 23, Female = 24	Total= 47
Age (year)	Range = 3-14	Mean = 8.3
Age of epilepsy onset (year)	Range =1-11	Mean = 3.3
Duration of epilepsy (year)	Range = 3-11	Mean = 5.1
Seizure frequency (per month)	Range = 4-350	Mean = 78.3
Past antiepileptic drugs (number/ patient)	Range = 4-12	Mean = 6.7
Etiology	Idiopathic or cryptogenic=31, Symptomatic = 9	Total = 40 (7 patients dropped out)

Table III. Efficacy of Lamotrigine after 3 months.

Seizure free (>90% reduction in seizure frequency)	N=8 (20%)
Improved (50-90% reduction in seizure frequency)	N=13 (32.5%)
Unchanged	N= 17 (42.5%)
Worsened (>25% increase in seizure frequency)	N=2 (5%)

dium valproate, ethosuximide, acetazolamide, benzodiazepines and steroids. Some patients received new AEDs such as vigabatrin and gabapentin, unsuccessfully.

Seven patients dropped out before the end of the trial. 2 of 7 dropped out during titration period upon parental request due to lack of initial improvement and 5 of 7 patients developed rashes during the LTG treatment leading to it's discontinuation. These patients (with rashes) were included in the safety analysis but excluded from the efficacy one.

Efficacy analysis

Forty patients were included in the efficacy analysis. Overal results of the trial are shown in Table III.

A greater than 50% decrease in seizure frequency vs. baseline was found in 21 patients (52.2%). In regard of drug efficacy in controlling the seizure, the best results were obtained with absence as 5 patients with absence became seizure free.

Nine of 15 patients with LGS (60%) had >50% reduction in seizure frequency. Poor results were noted in symptomatic partial seizures; only 1 of 5 such patients improved, in 2 of them seizure frequency remained unchanged, and the other 2 became worse.

Safety analysis

Five patients developed skin rashes which were confluent, erythematous and associated with fever; these patients were hospitalized and LTG was discontinued which led to full recovery. All of these patients were taking concomitant valproate.

Analysis of hematologic and biochemical parameters showed no significant changes over 4 months of LTG treatment.

DISCUSSION

Pediatric experience with LTG is relatively well established.[5-6.7,8,9,12,14,15] In a multicenter study, the efficacy of LTG was assessed in 285 children, and seizure frequency was reduced by >50% in one-third of patients. LTG was effective in all seizure types particularly for typical and atypical absence seizures.[12] In another study, the efficacy of LTG was assessed in 120 children with refractory epilepsy; 47.4% of them had >50% reduction in seizure frequency, and the best response was obtained in absence and LGS.[6] A multicenter placebo-controlled double blind trial demonstrated LTG efficacy against absence seizures and seizures associated with Lennox-Gastaut syndrome.[13]

In our study 52.5% of patients treated with LTG for 3 months had >50% decrease in the number of seizures; 8 of them became seizure-free. The best results were obtained in typical absence, as all of the patients with this kind of seizure were resistant to valproate, ethosuximide and benzodiazepines alone and in combination, but all of them (5 of 5) became seizure-free when LTG was added to the drug regimen.

Improvement was well maintained during the treatment period . These findings are in agreement with previously mentioned studies.[5-6-7-8-9-12-14-15]

Sixty percent (9 of 15) of patients with LGS had a reduction >50% in seizure frequency (responders) with LTG adjunctive therapy. In an open, add-on study on LGS Donaldson et al.[14] reported that 8 of 15 patients (53%) showed a >50% reduction with LTG. Timmings et al.[15] reported that 10 of 11 patients (91%) responded. In a double blind placebo-controlled trial 33% of patients with LGS had > 50% reduction in seizure frequency.[16]

Confirming the efficacy and safety of LTG for patients with LGS is important since there are few effective medications available for such patients. For many years valproate and benzodiazepines were frequently the mainstays of therapy. Felbamate has demonstrated efficacy in controlling seizures in LGS, but unfortunately felbamate use is limited by its reported association with aplastic anemia and hepatotoxicity.[17] Our findings provide evidence that LTG is a valuable new AED in the treatment of LGS.

Lamotrigine was reported to be poorly effective in intractable partial epilepsy.[18] In present series, few patients (5%) with symptomatic partial epilepsy experienced an increase in seizure frequency. This finding was also confirmed in other studies[6,18] but in contrast in a recent article, LTG was found to be effective in 38% of children with severe partial epilepsy.[8] These controversial results indicate a need for multi-center, double-blind placebo controlled trials of adjunctive LTG therapy in patients with partial epilepsy.

Five patients (10.6%) had to be hospitalized for a whole body rash which was confluent, erythematous and resolved with discontinuation of LTG. The incidence of

rash in this study is consistent with other reports.[6,14,16] The frequency of rash increases with more rapid titration and with concomitant valproate. Currently it is recommended to start LTG with low dose and slow titration.[19]

In conclusion, Lamotrigine can be considered a useful drug in the therapeutic armamentarium for childhood drug resistant epilepsy, especially for absence seizures and LGS.

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