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 occurred 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.


Keywords: Lamotrigine, refractory epilepsy, add-on therapy.

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.²,³ In addition, LTG has demonstrated its efficacy in pediatric patients with drug-resistant epilepsies including partial, myoclonic, absence,
Lamotrigine for Drug-Resistant Epilepsy

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 February 1998. 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 2 mg/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).

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 I. Lamotrigine titration according to concomitant AED.

<table>
<thead>
<tr>
<th>Week</th>
<th>Valproate</th>
<th>Other AEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 mg/kg/day</td>
<td>2 mg/kg/day</td>
</tr>
<tr>
<td>2</td>
<td>2 mg/kg/day</td>
<td>5 mg/kg/day</td>
</tr>
<tr>
<td>3</td>
<td>3 mg/kg/day</td>
<td>8-10 mg/kg/day</td>
</tr>
<tr>
<td>4</td>
<td>4-6 mg/kg/day</td>
<td>12-15 mg/kg/day</td>
</tr>
</tbody>
</table>

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

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

Table III. Efficacy of Lamotrigine after 3 months.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure free (&gt;90% reduction in seizure frequency)</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Improved (50-90% reduction in seizure frequency)</td>
<td>13 (32.5%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Worsened (&gt;25% increase in seizure frequency)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

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.\(^{6,18}\) In contrast, in a recent article, LTG was found to be effective in 38% of children with severe partial epilepsy.\(^5\) 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
Lamotrigine for Drug-Resistant Epilepsy

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.

REFERENCES