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EFFICACY AND SAFETY OF LAMOTRIGINE AS ADD-ON THERAPY IN 132 CHILDREN AND ADULT IRANIAN PATIENTS WITH TREATMENT-RESISTANT EPILEPSY

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ABSTRACT

This study was initiated to evaluate the long-term safety, tolerability and efficacy of seizure control of lamotrigine (LTG) in children and adult patients with partial seizures (PS) with or without secondary generalized seizure. A total of 132 patients (age 5-41 years) with treatment-resistant epilepsy received LTG as add-on therapy for up to four years. Overall, patients were treated with LTG for 27-226 weeks. The global assessment of seizure control compared to the three-month period before starting LTG treatment indicated that seizure control was gradually maintained during long-term LTG treatment for up to four years. The medical history of 23 patients who had a significant decrease in the number of seizures with LTG treatment indicated a subjective improvement in behavior, alertness, and quality of life. All 132 patients who received LTG as add-on therapy had used 2-4 anti-convulsive medications 2-7 years before entering this open continuation study. Patients had 7-45 seizures per month throughout the 3 months before entering this study. The overall decrease in the number of seizures was 58% after patients started receiving LTG. LTG was well tolerated. The majority of adverse effects were classified as being mild in intensity and only 5 patients (4%) were withdrawn from the study due to adverse effects (skin rash).

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INTRODUCTION

LTG is a broad-spectrum anti-epileptic drug (AED) which acts primarily via blockade of sodium channels to stabilize the neuronal membrane and inhibit the release of excitatory neurotransmitters, principally glutamate. LTG is effective as add-on therapy in children and adult patients with partial and secondary generalized seizures[4,12] not satisfactorily controlled with other anti-epileptic drugs. It seems to be less sedative than other anticonvulsant medications[16] and has an elimination half-life of longer than 24 hrs,[6] so once or twice daily dosage is possible in all patients.

PATIENTS AND METHODS

This study used an open design in which LTG was added to pre-existing anti-epileptic medication. Seizure types were classified according to the international classification of epilepsy, and patients with any type of refractory seizure were admitable. 63% of patients had two or more seizure types. The median age of seizure onset was 3.9 years and 17% of patients had a history of status epilepticus. 31% of patients had some degree of developmental impairment and behavioral problems at the time of entry. A 3 month baseline period during which daily seizure counts for each seizure type were recorded in a diary by the patient's parent or

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Table I. Total duration of LTG therapy.

LTG treatment period (weeks)	Number of patients (%)
• 24-48	7
• 48-72	8
• 72 - 96	10
• 96 - 120	12
• 120 - 144	16
• 144-168	18
• 168 - 192	24
• 192 - 216	37

Table II. Demographic characteristics.

• Male patients	55 (42 %)
• Female patients	77 (58 %)
• Total number of patients	132
• Mean age (years)	14.6 (5-41)
• Mean duration of epilepsy (years)	3.9 (2-7)
• Mean number of concomitant AED's	2.6 per patient

Table III. Concomitant anticonvulsive medication.

AED	N	Mean dose (mg)	Range (mg)
Phenobarbital	78	92.3	30 - 200
Phenytoin	41	212.6	50 - 600
Sodium valproate	64	1332.5	200 - 2600
Carbamazepine	71	720.4	200 - 1800
Clonazepam	48	4.6	0.2 - 20

guardian was followed by open label treatment with LTG. There was no dosage changes of concomitant AED's. Efficacy was assessed at the end of each of four successive 12 -week periods of therapy and the results were compared with baseline data. The principle measurement of efficacy was based on seizure frequency at the onset of the trials. The LTG dose was individualized according to body weight and the patients' concomitant anti-epileptic drug therapy. The doses were higher for patients taking enzyme inducing drugs (e.g., phenytoin, phenobarbital, carbamazepine), lower for those taking valproate and intermediate when a combination of enzyme-inducing drugs and valproate was being taken. LTG therapy was initiated at a dose of 2 mg/kg per day for patients not receiving valproate. Dosage was then gradually increased to a maximum of 15 mg/kg per day (or 400 mg/day) for patients not receiving valproate.

The medical history of each patient had already been documented for the previous 12 months of the study. This included details of seizure etiology, type and frequency and age at first seizure. Patient demographic data was also recorded. Data concerning birth, sex, height and weight were reviewed in each visit. Standard physical and neurological examinations including fundoscopy were performed. In addition, hematological and biochemical assessment was conducted and repeated every 3 months. Adverse effects since the last documented visit were recorded with respect to intensity, seriousness of action taken and whether they were attributable to LTG.

Written informed consent was obtained from all patients and from the parent or guardian if the patient was younger than 18 years or had a degree of learning disability.

RESULTS

Patient population

A total of 132 patients (77 male and 55 female) entered the continuation study. At the start of the study, 8% of the patients were between 5 to 10 years of age, 76% were 10-18 and 18% were above 18 (up to maximum 41 years).

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Table IV. Evaluation of efficacy of LTG by type of seizure.

Type of seizure	No. (%)	Average number of seizures per month before taking LTG	Average number of seizures per month after taking LTG
Simple partial seizure	21(16)	24	9
Complex partial seizure	47(36)	17	6
Partial seizure with secondary generalized seizure	64(48)	38	18
Total		79	33

Table V. Adverse effects.

Adverse effect	No. (%) of patients
Rash (no Stevens Johnson syndrome)	23 (17.4%)
Headache	17 (12.8%)
Somnolence	15 (11.3%)
Dizziness	14 (10.6%)
Asthma	12 (9%)
Nausea, vomiting	11 (8.3%)
Sleepiness	9 (6.8%)
Ataxia	8 (6.1%)
Flu-like symptoms	7 (5.3%)

According to the physical and neurological examination at the screening visit, 23% of patients had some degree of developmental impairment and behavioral problem. The study showed a 58% decrease in the number of seizures with LTG, and paired t-test indicated this amount to be statistically significant ($p<0.05$), with no serious clinical or laboratory documented side effect.

Treatment

A summary of duration of LTG treatment is given in Table I.

DISCUSSION

The inability of existing antiepileptic drugs to control seizures in up to 25% of patients with epilepsy underscores the urgent need for continued development of new antiepileptic agents. For practical and ethical reasons, new AED's are initially tested by addition to existing drugs in patients with refractory seizures. This situation introduces an important bias in the evaluation of drug efficacy. All patients included in the present study were resistant to at least 3 first-line antiepileptic drugs. In the very resistant epileptic population represented in this study, the use of LTG as add-on therapy was effective in reducing total seizure frequencies in more than 50% of patients, which is consistent with available data from reliable updated studies (46-62%). Therefore, one may consider that lamotrigine is useful as add-on therapy in children and adult patients with partial seizures with or without secondary generalization, but is not effective in idiopathic epilepsy or as monotherapy.

CONCLUSION

LTG is effective as add-on therapy in patients with poorly controlled simple and complex partial seizures. The drug is well tolerated and causes no significant drug-attributable changes in laboratory safety measures.

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