Brief Report

Effects of Lamotrigine Monotherapy in Patients with Newly Diagnosed Juvenile Myoclonic Epilepsy: An Open-Label Study*

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ABSTRACT

Background: It is important that drug therapy for juvenile myoclonic epilepsy (JME), a lifelong disorder requiring long-term therapy, is effective and well tolerated with long-term use. Lamotrigine as monotherapy or adjunctive therapy has been demonstrated to be effective in reducing the frequency of partial and generalized seizures in short- and long-term studies in children, adolescents, adults, and elderly patients with epilepsy, including those with JME. With its tolerability profile and spectrum of efficacy, lamotrigine might be an appropriate option for newly diagnosed patients with JME, a possibility that has not been empirically assessed.

Objective: The aim of this study was to assess the efficacy and tolerability of lamotrigine monotherapy in patients with newly diagnosed JME.

Methods: This open-label study was conducted at 18 clinical sites across the United States. Patients aged ≥ 12 years with newly diagnosed JME and who had experienced at least 1 generalized motor seizure since diagnosis but were antiepileptic treatment-naïve or had received inappropriate treatment due to misdiagnosis were enrolled. During the first 8 weeks of the study, lamotrigine (25-mg or 100-mg tablets) was introduced (to a maximum dosage of 100–500 mg/d, based on instructions in the package insert and clinical response). This dose escalation was followed by a 24-week treatment phase during which lamotrigine dose could be adjusted as needed to achieve optimal clinical benefit. Efficacy end points included the rates of patients with a decrease from baseline of at least 50% in the frequency of myoclonic, tonic-clonic, and absence seizures; and the rate of patients with mild, moderate, or marked improvement from baseline in global clinical status as perceived by the investigators. Adverse events were recorded in patient diaries, and

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diary information was reviewed by study personnel at clinic visits. Results were analyzed using descriptive statistics.

Results: Twenty-nine patients (17 females, 12 males; mean [SD] age, 24.0 [11.3] years [range, 12–50 years]) were included in the efficacy analysis. During the lamotrigine monotherapy treatment period, 58% of patients experienced a reduction from baseline of at least 50% in days with myoclonic seizures, and 56% and 38% of patients experienced a reduction of at least 50% in the frequency of generalized tonic-clonic seizures and absence seizures, respectively. At week 24 of the monotherapy phase, investigators perceived that 72% of patients had shown mild, moderate, or marked improvement in global clinical status relative to the start of the study.

Conclusions: In this study, lamotrigine monotherapy given to patients with newly diagnosed JME was associated with a reduction in the frequency of seizures and improvement in global clinical status as rated by the investigators. Lamotrigine was generally well tolerated. (*Curr Ther Res Clin Exp.* 2005;66:230–237) Copyright © 2005 Excerpta Medica, Inc.

Key words: lamotrigine, juvenile myoclonic epilepsy, myoclonus, generalized tonic-clonic, seizure.

INTRODUCTION

Juvenile myoclonic epilepsy (JME), a lifelong disorder with a typical onset during early adolescence, affects ~10% of those with epilepsy (worldwide).^{1–3} The myoclonic, absence, and generalized tonic-clonic seizures in patients with JME are often refractory to treatment with older antiepileptic drugs, such as carbamazepine and phenytoin.^{2,4} Valproate is currently the preferred initial monotherapy for newly diagnosed patients with JME. After an initial trial of valproate, lamotrigine monotherapy is the treatment of choice for JME and other idiopathic epilepsies according to a 2001 consensus panel of 45 US epilepsy experts.⁵

Most of the published evidence for first-line use of valproate in JME derives from reports of clinical experience before newer therapeutic options such as lamotrigine were available.^{1,6–8} Whereas lamotrigine has broad-spectrum efficacy for partial and generalized seizures including those in patients with JME,^{8–16} it is generally better tolerated than valproate, which can adversely affect reproductive and endocrine function and is associated with adverse events such as edema, weight gain, and hair loss.^{1,5–8,17–19} The incidence of neurologic adverse events is lower with lamotrigine than with carbamazepine or phenytoin; lamotrigine has minimal impact on cognitive function; and it is not associated with weight gain.^{15,19} Given the tolerability profile of lamotrigine compared with valproate, lamotrigine may be an option for newly diagnosed patients with JME.

In this open-label, multicenter study, the efficacy and tolerability of lamotrigine monotherapy were assessed among patients with newly diagnosed JME who, prior to the study, had received no treatment or had received inappropriate treatment because of misdiagnosis.

PATIENTS AND METHODS

This open-label study was conducted at 18 clinical sites across the United States.

Inclusion and Exclusion Criteria

Patients aged ≥ 12 years, weighing at least 25 kg, having newly diagnosed JME (supported by documented clinical features and electroencephalography [EEG]), and who had experienced at least 1 generalized motor seizure (as defined in the International Classification of Seizures²⁰) since diagnosis were enrolled. Diagnostic features of JME were considered to include a characteristic EEG pattern of diffuse, bilateral, symmetric, and synchronous polyspike-and-wave complexes of 4 to 6 Hz; sudden mild to moderate myoclonic jerks of the shoulders and arms that usually occurred after awakening; tonic-clonic, clonic-tonic-clonic, and/or absence seizures in addition to myoclonus; and precipitation by photosensitivity, sleep deprivation, alcohol intake, and/or fatigue.²¹ Prior to the study, these patients had received no treatment or had received inappropriate treatment (ie, any medication other than valproate or lamotrigine) because of misdiagnosis. The study also enrolled patients who converted to lamotrigine monotherapy because of poor efficacy or tolerability of valproate monotherapy. The data from the latter group of patients are reported elsewhere²² and are not included in this report.

Patients were excluded from the study if they were perceived by the investigator to be an inappropriate candidate for therapy with lamotrigine; had used any investigational drug within 4 weeks of initiation of the study or had been previously exposed to lamotrigine; were being treated with >1 antiepileptic drug; were pregnant, breastfeeding, or attempting to become pregnant; adhered to a ketogenic diet; had severe organic disease; had a history of alcohol or other drug abuse or dependence; had a history of medication noncompliance as determined by the investigator; or planned during the study period to undergo vagal stimulation or surgery to control seizures. Females were enrolled only if they agreed to use an acceptable contraceptive method during the study or were incapable of bearing children. All patients or their parents or legal guardians provided written informed consent, and institutional review board approval of the study protocol was obtained from all study sites.

Study Phases

This study comprised 3 phases: (1) a 2-week screening phase, during which eligibility was verified and baseline physical and seizure assessments were obtained; (2) a dose-escalation phase lasting up to 8 weeks, during which lamotrigine (25-mg or 100-mg tablets) was introduced (to a maximum dosage of 100–500 mg/d, based on instructions in the package insert²³ and clinical response); and (3) a 24-week treatment phase, during which lamotrigine dose could be adjusted as needed to achieve optimal clinical benefit.

During the dose-escalation and treatment phases, patients or their parents/guardians were to record, in a daily diary provided to them, the number of

days on which the patient experienced myoclonus and the number of generalized tonic-clonic seizures and absence seizures. These measures were retrospectively determined for the 12 weeks prior to the screening visit to obtain baseline values against which to compare the study data. Because of the open-label nature of the study, patients who received at least 1 dose of study medication but who discontinued the study prematurely were considered treatment failures. Adverse events (defined as any untoward medical occurrence regardless of its suspected cause) were recorded in patient diaries. Clinic visits for the review of diaries, adverse events, and concomitant medication use occurred during the screening phase and at weeks 1, 12, and 24 of the treatment phase. Adverse events were recorded throughout the study, beginning on the day after screening. Any serious adverse events that were unresolved at the last study visit were followed up until the event resolved or stabilized, the patient was lost to follow-up, or the event was otherwise explained.

On weeks 1, 12, and 24 of the treatment phase, investigators rated patients' global clinical status and their status on the following specific indices: seizure frequency, seizure duration, seizure intensity, adverse events, social functioning, intellectual functioning, and motor functioning. Global clinical status was rated by investigators as marked, moderate, or mild deterioration; no change; or marked, moderate, or mild improvement. At weeks 1, 12, and 24 of the treatment phase, patients rated their satisfaction with therapy as much better, somewhat better, the same as, somewhat worse, or much worse than prestudy therapy. Power analysis was not undertaken for this study.

RESULTS

Twenty-nine patients (17 females, 12 males; mean [SD] age, 24.0 [11.3] years [range, 12–50 years]) received at least 1 dose of lamotrigine. During the treatment phase, the mean lamotrigine maintenance dosage was 317.6 mg/d (range, 100–500 mg/d). Nine patients (31%) withdrew prematurely from the study (**Table**). The primary reason for premature discontinuation was adverse events (4 patients [14%]) (discussed later).

The median monthly frequencies of seizures at baseline in all patients who enrolled in the study were 5.0, 0.3, and 8.0 for days with myoclonus, number of generalized tonic-clonic seizures, and number of absence seizures, respectively. Over the lamotrigine treatment period, 58% of patients experienced a reduction from baseline of at least 50% in days with myoclonic seizures, and 56% and 38% of patients experienced a reduction of at least 50% from baseline in frequency of generalized tonic-clonic and absence seizures, respectively (**Figure**). Two patients (7%) experienced an increase of >25% from baseline in the frequency of myoclonus during the treatment phase.

At week 24 of the treatment phase, investigators perceived that 72% of patients had shown mild, moderate, or marked improvement in global clinical

Table. Baseline demographic and clinical characteristics of the study patients (N = 29).

Characteristic	Value
Age, y	
Mean (SD)	24.0 (11.3)
Range	12–50
Sex, no. (%)	
Female	17 (59)
Male	12 (41)
Race, no. (%)*	
White	21 (72)
Black	3 (10)
Other	5 (17)
Study completers, no. (%)	20 (69)
Discontinued, no. (%)	9 (31)
Adverse event	4 (14)
Lost to follow-up	3 (10)
Protocol violation	2 (7)

*Percentages do not total 100 due to rounding.

Figure. Percentages of patients with a $\geq 50\%$ reduction in seizures from baseline, by seizure type.

status relative to the start of the study. The rates of patients perceived to be mildly, moderately, or markedly improved from baseline on the 7 specific status indices were as follows: seizure frequency (69%), seizure intensity (66%), seizure duration (62%), social functioning (41%), motor functioning (34%), adverse events (31%), and intellectual functioning (31%).

On their final visit, 92% of patients indicated that they were mildly, moderately, or highly satisfied with the study medication.

In the 29 patients who received at least 1 dose of lamotrigine, adverse events that investigators considered to be at least possibly related to study medication were dizziness (5 patients [17%]); headache (4 [14%]); somnolence (3 [10%]); amnesia, asthenia, nausea, and vomiting (2 patients [7%] each); and tremor, insomnia, cognitive abnormality, emotional lability, confusion, depression, apathy, nervousness, abdominal pain, dyspepsia, contact dermatitis, leukopenia, weight increase, arthralgia, arthritis, myalgia, and rhinitis (1 patient [3%] each).

Four patients (14%) withdrew from the study prematurely because of adverse events, including increased generalized seizures, arthralgia/myalgia, coma (secondary to drowning after having a seizure), and viral-like illness (1 patient [3%] each).

DISCUSSION

In this study, lamotrigine monotherapy given to patients with newly diagnosed JME was associated with a reduction in seizure frequency and improvement in clinical status as rated by investigators.

The results of this investigation should be interpreted in the context of its limitations, which preclude drawing conclusions about the role of lamotrigine in the clinical improvements. First, the study employed an open-label design. Therefore, the degree to which improvements can be attributed to study medication is uncertain. Second, the sample size of the study was small. Third, the study employed retrospective baseline data. Seizure counts from memory may be inaccurate and may underestimate or overestimate seizure frequency. Despite these limitations, the data are encouraging in their consistency with previous results^{8,9,11,14,22} from studies in patients with JME and other idiopathic epilepsy syndromes.^{2,3} These findings corroborate reports of the efficacy and tolerability of lamotrigine in patients with JME converting from valproate therapy.^{8,9,11,14,22} For example, seizures were controlled, and the valproate-associated adverse effects of edema, weight gain, and hair loss were reduced or eliminated in 12 patients with JME who switched from valproate to lamotrigine or who added lamotrigine to a regimen containing a reduced valproate dose.⁸

CONCLUSIONS

In this open-label study, lamotrigine monotherapy given to patients with newly diagnosed JME was associated with a reduction in the frequency of seizures and

improvement in global clinical status as rated by the investigators. Lamotrigine was generally well tolerated.

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REFERENCES

1. Dreifuss FE. Juvenile myoclonic epilepsy: Characteristics of a primary generalized epilepsy. *Epilepsia*. 1989;30(Suppl 4):S1-S7, discussion S24-S27.
2. Grünewald RA, Panayiotopoulos CP. Juvenile myoclonic epilepsy: A review. *Arch Neurol*. 1993;50:594-598.
3. Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: A 5-year prospective study. *Epilepsia*. 1994;35:285-296.
4. Dasheiff RM, Ritaccio AL. Characterization of intractable juvenile myoclonic epilepsy: New perspectives on primarily generalized seizures. *Seizure*. 1993;2:11-19.
5. Karczeski S, Morrell M, Carpenter D. The Expert Consensus Guideline Series: Treatment of epilepsy. *Epilepsy Behav*. 2001;2:A1-A50.
6. Jeavons PM, Clerk JE, Maheshwari MC. Treatment of generalised epilepsies of childhood with sodium valproate. *Dev Med Child Neurol*. 1977;19:9-25.
7. Delgado-Escueta AB, Enrile-Bacsal FE. Juvenile myoclonic epilepsy of Janz. *Neurology*. 1984;34:285-294.
8. Buchanan N. The use of lamotrigine in juvenile myoclonic epilepsy. *Seizure*. 1996;5:149-151.
9. Timmings PL, Richens A. Efficacy of lamotrigine as monotherapy in juvenile myoclonic epilepsy: Pilot study results. *Epilepsia*. 1993;34(Suppl 2):160.
10. Brodie MJ, Richens A, Yuen AWC, et al. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. *Lancet*. 1995;345:476-479.
11. Sharpe C, Buchanan N. Juvenile myoclonic epilepsy: Diagnosis, management and outcome. *Med J Aust*. 1995;162:133-134.
12. Reunanen M, Dam M, Yuen AWC. A randomized open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. *Epilepsy Res*. 1996;23:149-155.

13. Gilliam F, Vazquez B, Sackellares JC, et al. An active-control trial of lamotrigine monotherapy for partial seizures. *Neurology*. 1998;51:1018–1025.
14. Gericke CA, Picard F, de Saint-Martin A, et al. Efficacy of lamotrigine in idiopathic generalized epilepsy syndromes: A video-EEG-controlled, open study. *Epileptic Disord*. 1999;1:159–165.
15. Matsuo F. Lamotrigine. *Epilepsia*. 1999;40(Suppl 5):S30–S36.
16. Steiner TJ, Dellaportas CI, Findley LJ. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: A double-blind comparison with phenytoin. *Epilepsia*. 1999;40:601–607.
17. Isojärvi JT, Laatikainen TJ, Knip M, et al. Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol*. 1996;39:579–584.
18. Murialdo G, Galimberti CA, Gianelli MV, et al. Effects of valproate, phenobarbital, and carbamazepine on sex steroid setup in women with epilepsy. *Clin Neuropharmacol*. 1998;21:52–58.
19. Biton V, Mirza W, Montouris G, et al. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. *Neurology*. 2001;56:172–177.
20. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389–399.
21. Delgado-Escueta AV, Serratosa JM, Medina MT. Juvenile myoclonic epilepsy. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practice*. 2nd ed. Baltimore, Md: Williams & Wilkins; 1997:484–501.
22. Morris GL, Hammer AE, Kustra RP, Messenheimer JA. Lamotrigine for patients with juvenile myoclonic epilepsy following prior treatment with valproate: Results of an open-label study. *Epilepsy Behav*. 2004;5:509–512.
23. Lamictal (lamotrigine) tablets [package insert]. Research Triangle Park, NC: Glaxo-SmithKline; 2004.

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