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Lamotrigine Therapy of Epilepsy in Tuberous Sclerosis

*†David Neal Franz, *†Cynthia Tudor, *†Jennifer Leonard, *‡John C. Egelhoff, *†Anna Byars, *Kristin Valerius, and ‖Gopalan Sethuraman

*Departments of *Pediatrics, †Neurology, ‡Radiology and ‖Environmental Health, University of Cincinnati College of Medicine, Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.*

Summary: *Purpose:* Lamotrigine (LTG), a newer antiepileptic drug (AED), has activity against both partial-onset and generalized seizures. Its reported benefits for behavior, and its effectiveness in Lennox–Gastaut syndrome and other forms of refractory epilepsy, make it a logical choice for treatment of epilepsy in tuberous sclerosis complex (TSC). We present our experience with LTG therapy of epilepsy in 57 patients with TSC.

Methods: Patients fulfilled the diagnostic criteria for clinically definite TSC. LTG was initiated and increased until improvement in seizure frequency was noted, intolerable side effects occurred, or maximal doses were reached. Seizure frequency and behavioral changes were recorded during LTG therapy and compared with those prior to the introduction of LTG.

Results: Twenty-four (42%) were seizure free, and 21 (37%) had a >50% reduction in seizure frequency. Eighteen (32%) had subjectively improved behavior and/or alertness with daily activities. Thirty-eight (67%) had no change in this regard, whereas one (2%) became worse. Responders were more likely to not have a history of infantile spasms, and to have experienced only partial seizures ($p < 0.05$). Otherwise no phenotypic correlations with response were apparent.

Conclusions: Among patients with TSC and epilepsy, LTG was effective and well tolerated, including as initial monotherapy. Improved alertness and behavior were apparent in many patients. The incidence of side effects is similar to that reported for other pediatric populations with symptomatic partial epilepsy. The usefulness of LTG in TSC may relate to an underlying defect of glutamatergic neurotransmission in partial epilepsy. **Key Words:** Tuberous sclerosis—Lamotrigine—Epilepsy—Infantile spasms—Partial seizures.

Lamotrigine (Lamictal; LTG) is one of the newer antiepileptic drugs (AEDs), and has activity against both partial-onset and generalized seizures. Its mechanism of action is thought to involve blockade of voltage-sensitive sodium channels, and thereby inhibition of release of excitatory neurotransmitters. It appears to have less potential for cognitive slowing/impairment than many of the traditional AEDs (1) Anecdotally, LTG has been reported to be beneficial for self-injurious and autistic behaviors, either with or without concurrent epilepsy. It also has been used for purely psychiatric indications, for example, as a mood-stabilizing agent (2). Pediatric experience consists largely of case reports and uncontrolled, open-label trials, primarily in children with refractory seizures (3,4).

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder that exhibits a marked degree of phenotypic variability. Two distinct genetic loci can produce the TS phenotype, chromosome 9q34 (TSC1, protein product: hamartin) and 16p13 (TSC2, protein product: tuberin). Once thought to be relatively uncommon, TSC is now believed to have an incidence of as much as 1 in 6,000 and a prevalence of 1 in 10,000. As many as 90% of affected individuals have seizures, and about one third develop infantile spasms. Intractable epilepsy develops in many, particularly among those with infantile spasms (5–7).

Vigabatrin (VGB) is an irreversible inhibitor of γ-aminobutyric acid (GABA) transaminase. This agent, which is not approved for use in the United States, has remarkable efficacy against infantile spasms in TSC. A recent meta-analysis a reported seizure-free response rates of 95% (8). It may be that other of the newer AEDs have specific benefits, or toxicities, in TS patients, distinct from other children with epilepsy. TSC also is frequently associated with cognitive impairment, autism, and behavior problems. These difficulties are often aggravated or compounded by poorly controlled seizures, as well as by medication side effects. The reported benefits of LTG for behavior, and its known effectiveness in patients with Lennox–Gastaut syndrome and other forms

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Address correspondence and reprint requests to Dr. D.N. Franz at Neurology/OSB-5, Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, U.S.A. E-mail: d.franz@chmcc.org

of refractory epilepsy (9–11), make it a logical choice for treatment of epilepsy in this population. We present our experience with LTG therapy of seizures in 57 patients with TS. All are monitored in the multidisciplinary TS and/or comprehensive epilepsy program at Children's Hospital Medical Center.

METHODS

All patients fulfilled the diagnostic criteria for clinically definite TS, as defined by the diagnostic criteria committee of the National Institutes of Health (NIH) Consensus Conference on Tuberous Sclerosis held in Annapolis, Maryland, in 1998 (6). Patients received periodic screening assessments as set forth by this conference based on clinical indications. These included magnetic resonance imaging (MRI) of the brain, cardiac and renal ultrasound, neuropsychologic assessment, and physician evaluations. One neuroradiologist (J.C.E.) evaluated all cerebral MRI scans according to number and location of tubers, subependymal nodules, vascular abnormalities, as well as any additional migrational defects. Fifteen patients were initially enrolled as a part of an unrandomized open-label trial. Subsequent patients were treated on clinical grounds, using the same titration schedule and follow-up evaluations. Side effects were ascertained by interview and physical examination at each follow-up visit and after titration was completed. Formal neuropsychologic evaluations were performed as clinically indicated. However, standardized measurements of behavior/cognitive function were not available in a sufficient number of patients to assess objectively the effects of LTG.

LTG pharmacokinetics vary significantly depending on concomitant pharmacotherapy. Valproate (VPA) extends the half-life ($T_{1/2}$) of LTG to $\geq$70 h. Enzyme-inducing AEDs shorten $T_{1/2}$ to 12 h. In patients receiving both VPA and an enzyme inducer, these effects cancel each other out, resulting in a $T_{1/2}$ of ~27 h, similar to that of LTG monotherapy (24–37 h).

In children, Chen et al. (12) reported a mean $T_{1/2}$ of 32 h in subjects aged 3.8 to 11.3 years receiving LTG as monotherapy, similar to that observed in adults. Pharmacokinetics were linear. No gender differences in metabolism were noted. Volume of distribution was 1.50 ± 0.51 L/kg, and oral clearance was 0.64 ± 026 ml/min/kg, both higher than observed in adults. This suggests that children receiving LTG will tolerate dosing intervals similar to those in adults, but may require higher dosages to produce an equivalent pharmacologic effect.

LTG therapy was instituted in the following manner.

1. Patients receiving an enzyme-inducing AED: Initial dose, 1.0 mg/kg/day; increment, 1.0 mg/kg every 7 days. Maximal dose, 15 mg/kg/day.
2. Patients receiving VPA: Initial dose, 0.2 mg/kg/day; increment, 0.2 mg/kg every 14 days. Maximal dose, 4–5 mg/kg/day.
3. Patients receiving VPA and an enzyme-inducing AED or starting LTG as monotherapy. Initial dose, 0.5 mg/kg/day. Increment, 0.5 mg/kg every 7 days. Maximal dose, 15 mg/kg/day.
4. Dosage was increased until either improvement in seizure frequency was noted, intolerable clinical side effects occurred, or the maximal dose was reached. In cases with an inadequate response despite achieving the maximal dose, trough serum LTG levels were measured. If the level was <15 μg/ml *and* there were no signs of clinical toxicity, further titration was undertaken. End points were either seizure control, intolerable side effects, or level >15 μg/ml without adequate response.

If patients tolerated this titration schedule, and experienced improvement in seizure control, previous medications were tapered and discontinued. Parents were asked to keep records of their child's seizure frequency, as is our standard practice. At each follow-up visit and at the end of titration, parents were asked if any change in their child's behavior, sleep patterns, and level of alertness had been noted. At the end of titration, patients were divided into three groups based on parental record keeping of seizure frequency: 1, No change (i.e., 0–49% decrease from baseline); 2, >50% reduction (i.e., 50–99% decrease from baseline); and 3, Seizure free (i.e., 100% decrease from baseline).

Children with a >50% reduction in seizure frequency were considered responders, whereas those that did not were considered nonresponders. Differences in the two groups were analyzed by using standard statistical techniques such as analysis of variance (ANOVA).

Data analysis

A logistic regression proportional odds model was fit to the data to explore the combination of variables that best explained the classification of subjects as a (1) Nonresponder, (2) 50–99% Seizure reduction responder, and (3) >99% Seizure reduction responder (seizure-free responder). The variables used for the model included both qualitative nominal variables Gender (Male, Female), Infantile Spasms (Yes, No), Partial Seizures (Yes, No), and quantitative variables (Age at Diagnosis, Age at Onset, and Duration of Lamictal). For the qualitative nominal variables included in the model, proportional odds ratios measured the proportional odds of being a responder (seizure free or otherwise) compared with a nonresponder for each level of the variable. Additionally, for quantitative variables ANOVA was performed to assess significant differences among the response levels for the quantitative variables. All analyses were performed using the Statistical Analysis System (SAS) software.

RESULTS

Fifty-seven patients with tuberous sclerosis were treated with LTG (Table 1). They ranged in age from 5 months to 35 years, with a mean age of 9.1 ± 9.0 years, and consisted of 32 male and 25 female subjects. Twenty-six patients had exclusively partial seizures. Thirty-one were either having infantile spasms at the time LTG was added, or had experienced them in the past. Five patients had Lennox–Gastaut syndrome in addition to TSC. Twenty-four (42%) became seizure free, 21 (37%) had a >50% reduction in seizure frequency, and 12 (21%) had <50% reduction. Of those children who had experienced infantile spasms, nine became seizure free, 12 had a >50% reduction, and 10 did not respond. Eighteen (32%) were thought to have improved behavior, alertness with daily activities, or both. Thirty-eight (67%) experienced no change in this regard, and one (2%) became worse. Twenty-six of the responders received LTG as monotherapy. In nine responders and in one nonresponder, it was used as initial monotherapy for partial epilepsy (i.e., as the first AED for new-onset seizures). The remaining 17 were converted to LTG monotherapy after having first received other AEDs (Table 2). The remaining 16 responders received LTG in combination with one or more AEDs. Average LTG doses at the end of titration were not significantly different between responders (9.6 mg/kg/day ± 5.7) and nonresponders (8.5 mg/kg/day ± 5.6). A total of 11 children had serum LTG levels <15 μg/ml after reaching the initial maximal dose. They subsequently underwent further dose escalation as outlined earlier. Eight of these children ultimately responded to LTG, three did not.

LTG response was sustained over time. As of May 2000, the most recent date for which information was available on all patients, responders took LTG an average of 25.7 months (median, 20 months). Nonresponders took LTG an average of 9.6 months (median, 4 months). Cerebral and cerebellar tuber counts were available on 33 patients.

Responders had a mean of 12.2 ± 5.5 cerebral tubers and 0.4 ± 0.8 cerebellar tubers. Nonresponders had 14.8 ± 4.7 cerebral and 0.4 ± 0.7 cerebellar tubers.

TABLE 1. *Characteristics of all participants*

Mean age at treatment	9.1 yr
Median age at treatment	7.0 yr
Male	32 (56%)
Female	25 (44%)
History of infantile spasms	33 (58%)
Behavior improvement	18 (32%)
Sporadic TSC	44 (77%)
Familial TSC	13 (23%)
Autism	22 (43%)
LTG monotherapy	25 (46%)
Any mental handicap	42 (74%)
Avg. no. tubers	14

TSC, tuberous sclerosis complex; LTG, lamotrigine.

Three (5%) children developed a cutaneous rash. In one case an erythema multiforme type exanthem was noted, in association with a decreased platelet count and elevated serum transaminases. No mucocutaneous lesions or other laboratory abnormalities were noted. The rash and laboratory abnormalities resolved with discontinuation of the drug. In the other two children, the rash resolved spontaneously without decrease in dosage.

One of these remains on LTG with continued positive effects. The other was subsequently taken off LTG owing to complaints of headache.

One patient died while under treatment. She had a history of intractable epilepsy and severe autism, which necessitated institutional care. After experiencing >50% reduction in seizure frequency and behavioral improvement, she was found dead in her bed. She was receiving carbamazepine (CBZ) and clonazepam (CLZ) in addition to LTG. Autopsy found no evidence of hepatic dysfunction, pulmonary edema, or cutaneous reaction. Death was attributed to SUDEP (sudden unexplained death in epilepsy). One (2%) patient was taken off the medication owing to behavioral deterioration. This individual initially had improved behaviors coincident with a >50% reduction in seizure frequency when LTG was begun, but experienced worsening behaviors when dosage was increased >1.5 mg/kg/day. This was not associated with deterioration in seizure control. Behavioral disturbances consisted of agitation, restlessness, and increased autistic features. Return to a lower dosage did result in any improvement, and LTG was eventually discontinued. No other side effects requiring modification of therapy were seen. Responders were more likely not to have had infantile spasms than nonresponders (odds ratio, 4.3; 95% confidence interval, 1.4–13.2). Similarly, there was a trend for responders to have had only partial and complex partial seizures during their lifetime; however, this did not reach significance (odds ratio, 1.5; 95% confidence interval, 0.16–13.7). All the patients with subjective improvements in behavior were also responders. Twelve of the 18 with improved behavior in fact became seizure free. All of the nonresponders exhibited no subjective change in behavior. This suggests that improvements in behavior, when they occur, may relate to improved seizure control. No correlation was found between response and number or location of MRI lesions, number or type of previous AEDs, severity of cognitive impairment, or any other characteristics.

Seizure-free responders were significantly more likely to have a later age of onset of epilepsy (16.4 months ± 16.6) than other responders (5.5 months ± 5.4) and nonresponders (4.4 months ± 4.2) (Student–Newman–Keuls test, $p < 0.05$). Seizure-free responders were also more likely to have been taking LTG longer (34.0 months ±

TABLE 2. *Lamotrigine response and patient characteristics*

	<50% reduction in seizures	>50% reduction in seizures	Seizure free
All patients (N = 57)	12 (21%)	21 (37%)	24 (42%)
Median age at treatment	1.8 yr	4.9 yr	8.5 yr
Age 0–5 yr	8	10	9
Age 6–12 yr	4	4	6
Age 13–18 yr	0	2	5
Age >18 yr	0	5	4
Male	7 (12%)	10 (18%)	15 (26%)
Female	5 (9%)	11 (19%)	9 (16%)
History of infantile spasms	10 (18%)	14 (26%)	9 (16%)
Behavior improvement	0	6 (11%)	12 (21%)
Sporadic TSC	11 (19%)	16 (28%)	17 (30%)
Familial TSC	1 (2%)	5 (9%)	7 (12%)
Diagnosis of autism	3 (5%)	10 (18%)	9 (16%)
LTG monotherapy	2 (4%)	7 (12%)	17 (30%)
Maximal dose	8.5 mg/kg/d ± 5.6	10.4 mg/kg/d ± 6.7	8.7 mg/kg/d ± 4.9
Any mental handicap	10 (18%)	17 (30%)	15 (26%)
Avg. # of tubers	15	13	12

TSC, tuberous sclerosis complex; LTG, lamotrigine.

26.5) compared with other responders (16.1 months ± 19.9) and nonresponders (10.6 months ± 12.6) (Student–Newman–Keuls test $p < 0.05$). A greater percentage of individuals with familial TSC responded (12 of 13 cases, 92%) than those having sporadic TSC (33 of 44 cases, 75%). This difference did not reach statistical significance, however ($p = 0.18$). Seizure-free responders were also compared with patients with persistent seizures but >50% reduction and with nonresponders. This may reflect the trend for a later onset of seizures to be associated with less severe epilepsy. Seizure-free responders, other responders, and nonresponders did not differ significantly with regard to history of infantile spasms, autism, tuber counts, or other characteristics.

DISCUSSION

This is the largest single center report of efficacy of a specific AED in individuals with TSC. Our experience with LTG in these patients suggests that it is safe, effective, and well tolerated for the treatment of epilepsy in this context. Response rates were favorable given the often intractable nature of epilepsy in this disorder. LTG response in our group was similar or superior to that reported in other pediatric populations with symptomatic partial epilepsy, as well as in Lennox–Gastaut syndrome (9–13). Limitations include lack of randomization or a control group. With the exceptions of VGB and topiramate (TPM), there are no data regarding response of epilepsy in TSC to specific AEDs. Efficacy of VGB in infantile spasms/TSC has already been described (8). Nabbout et al. (14) reported an initial responder rate (>50% reduction) of 85% in 32 children with TSC and partial epilepsy. Follow-up interval ranged from 3 to 5 months. Although subjects were followed up longer, response rates beyond this initial observation period were not reported for TSC patients. We have reported a responder rate (again >50% reduction) of 64% (nine of 14) in a group of TSC patients treated with topiramate (15). LTG also is suitable as initial monotherapy for partial epilepsy in TSC. Barron et al. (16) reported seizure freedom in 45% of 83 children treated with improved seizure control, reduction in dosage, or lamotrigine monotherapy. Behavioral improvements were seen in 25%, similar to our observations. Cognitive and behavioral improvements could reflect discontinuation of other medications with more prominent behavioral side effects, or a direct effect of LTG. Determination of serum AED levels can be useful, particularly when patients seem to be failing therapy. Serum concentrations may be lower than expected based on milligram per kilogram daily dose (16–18). Patients can benefit from continued dose escalation even after achieving the usual maximal recommended dosages.

Currently, routine laboratory monitoring is not recommended for patients receiving LTG (13). Headache, insomnia, incoordination of gait, diplopia, and exacerbation of seizures are more common adverse events. Most serious is the development of a potentially life-threatening rash, which is reported to occur in as many as 1 to 2% of pediatric patients. Stevens–Johnson syndrome, toxic epidermal neurolysis, as well as a hypersensitivity syndrome (sometimes without prominent cutaneous lesions), consisting of malaise, lymphadenopathy, hepatic dysfunction, and clinical shock, have occurred. Risk of rash appears at least partially related to overly rapid dose escalation, with fewer complications occurring with a slower titration schedule such as we used. Our observed incidence of side effects including rash is similar to or less than that reported for other pediatric populations (13,16). Only one of our patients had to discontinue LTG due to skin rash, and another due

to AED hypersensitivity syndrome. None experienced a potentially life-threatening rash such as Stevens–Johnson syndrome or toxic epidermal necrolysis.

With rare exceptions, individuals with TSC and epilepsy have either infantile spasms, partial seizures, or both. Children often have infantile spasms, and then develop partial seizures as they grow older (19). A retrospective analysis of 13 patients has suggested that developmental outcomes are improved in TSC with better seizure control, particularly with regard to infantile spasms (19). VGB demonstrates striking effectiveness (95% seizure-free response) for infantile spasms in this population (8). This finding strongly suggests an underlying GABAergic dysfunction in this epilepsy syndrome. Although not so dramatic as VGB, LTG has efficacy for partial seizures associated with TSC. The mechanism of action of LTG anticonvulsant effects is not fully understood, but appears to involve blockade of voltage-sensitive sodium channels. This results in inhibition of excitatory neurotransmitter release (chiefly glutamate but also aspartate) from presynaptic neurons. Effects on voltage-sensitive calcium channels may also contribute to decreased presynaptic glutamate release, as well as helping prevent excessive calcium influx and resultant neurotoxicity postsynaptically (13). Additionally, facilitation of presynaptic GABA release by LTG has recently been reported (20).

To date, the best-established phenotypic correlation in TSC is that of mental retardation with higher cerebral tuber counts (5). Age of seizure onset, extent of cerebral involvement, presence of autism, cognitive impairment, or abnormalities in other organ systems did not predict LTG response. In like fashion, infantile spasms and VBG response do not seem to correlate with particular phenotypic features. If LTG response is independent of specific characteristics, it may reflect a common neurobiologic derangement in partial epilepsy associated with TSC.

We speculate that epileptogenesis in TSC has two primary mechanisms, one involving GABAergic neurotransmission, which produces infantile spasms, and another involving glutamatergic neurotransmission, which is involved in partial epilepsy. Cortical dysplasia, histologically similar to that occurring in cerebral tubers, is known to be associated with abnormalities of GABA, *N*-methyl-D-aspartate (NMDA), and glutamate. Diminished expression of GABA receptors, elevated levels of NMDA and glutamate receptors, and abnormal expression of NMDA NR2A/B subunits, are some of the derangements that have been reported (21–23). Elevated levels of quinolinic acid, an NMDA-receptor agonist, have also been identified in epileptogenic cortex resected from patients with TSC (24). If true, this would support a strategy of using AEDs with primary action on excitatory amino acid neurotransmitters in TSC-associated partial epilepsy.

Although further study is needed to confirm these observations, our findings suggest that LTG is effective for partial epilepsy in TSC, either when it occurs by itself, or in association with infantile spasms. LTG should also be considered as initial monotherapy for children with TSC and partial epilepsy. Selected patients can benefit from more aggressive titration and/or higher doses than commonly administered.

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