Lamotrigine in children with refractory epilepsy

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We studied the efficacy and side effect profile of lamotrigine (LTG) in children with intractable epilepsy.

We reviewed the database of our prolonged video-EEG laboratory to screen patients with intractable epilepsy who were on LTG either alone or in combination for three months or more.

Of 75 patients, 28 patients (37%) had primary generalized seizures, 42 patients (56%) had partial onset seizures with or without secondary generalization, and 5 patients (7%) had two or more types of seizures. LTG reduced seizure frequency by at least 50% in 57.1% of patients with partial seizures and in 53.6% of patients with primary generalized seizures.

The incidence of adverse events was relatively low (15%); the most common was skin rash.

LTG should be considered in the treatment of pediatric patients with both partial onset and primary generalized seizures refractory to the major older antiepileptic drugs. LTG has a favorable side effect profile.

Key words: lamotrigine, intractable epilepsy, efficacy, side effect.

New generation antiepileptic medications have improved seizure outcome in patients with intractable epilepsy and seem to be superior in tolerability when compared with conventional antiepileptic drugs (AEDs). Lamotrigine (LTG) is a new AED that has effectiveness against both partial onset and generalized seizures[1-5]. LTG is approved by the Food and Drug Administration (FDA) as an adjunctive therapy for partial seizures in adults and in children older than two years as well as generalized seizures associated with Lennox-Gastaut syndrome[1-3]. LTG monotherapy is effective in newly diagnosed patients with partial and generalized tonic-clonic seizures[3,6-12]. It is indicated for conversion to monotherapy in adults with partial seizures receiving treatment with a single enzyme-inducing AED such as phenytoin or carbamazepine because of inadequate seizure control or adverse events[13,14]. LTG is also used in the treatment of self-injurious and autistic behaviors as a mood stabilizer drug[15-17]. Most patients with epilepsy receiving LTG reported an improvement in quality of life, cognition and mood[16-20]; these have been suggested to be independent of seizure reduction[19,20]. The blockage of presynaptic voltage-sensitive sodium channels, stabilization of neuronal membrane and inhibition of excitatory neurotransmitter release (e.g. glutamate and aspartate) is thought to be the mechanism of action of LTG[21]. LTG is generally well tolerated; the most common adverse effects are deterioration of seizure control and skin rashes, which can be life-threatening[22-25]. History of another AED-related rash and age younger than 13 years are reported to be the major risk factors for developing rash to LTG[25]. Other side effects include headache, dizziness and insomnia[22-24]. We studied the efficacy and side effect profile of LTG in pediatric patients with intractable seizure disorder.

Material and Methods

We reviewed the database of our prolonged video-EEG laboratory between 1994-2002 and determined 75 patients with refractory epilepsy

who had been on LTG either alone or in combination with other AEDs for at least three months or more. We reviewed the medical records of these patients retrospectively. For missing information, parents were interviewed by telephone. Data such as age, gender, age at seizure onset, seizure type, etiology, intelligence scores, neurologic deficits, family history for epilepsy and other neurological disorders, parental consanguinity, the period of the treatment with LTG either alone or in combination with other AEDs, the dosage of LTG, side effects, seizure outcome on LTG, cranial magnetic resonance imaging (MRI), and EEG findings were recorded. Seizures were classified according to the International Classification of Seizures[26] based on the review of videotaped attacks or clinical descriptions by parents. Clinical response to the treatment was evaluated by comparison of mean seizure frequency in the three months preceding and following LTG treatment initiation, respectively. The medication was considered as "effective" when all seizures had ceased or seizure frequency was decreased by ≥50% and "not effective" when seizure frequency was decreased by <50%, unchanged or worse.

Statistical Analysis

χ^2 test and Mann-Whitney test were utilized for statistical analysis.

Results

Patient Characteristics

Of 75 patients, 46 (61%) were male and 29 (39%) were female. The mean age of the patients at the time of video-EEG monitoring was 12.5±5.8 years (range: 1-24 years; median: 13 years). The mean age at seizure onset was 3.3±3.2 years (median: 3 years; range: newborn period-13 years). Seizure onset was in the newborn period in 4 patients (6%), between 1 month-1 year old in 28 patients (37%), between 1-5 years old in 24 patients (32%), and over 5 years old in the remaining 19 patients (25%).

Parental consanguinity was present in 20% (n: 15) of the patients, and a family history for epilepsy and/or mental retardation in 31% (n: 23). The most common cause was hypoxic and/or infectious insults during the perinatal period (n: 15). Other etiologic factors included malformations of the central nervous system, intracranial mass lesion (hamartoma/tumor), meningitis, encephalitis, head trauma, inborn metabolic disorders, chromosomal abnormalities, and intrauterine infection (Table I). Common associated findings were mental retardation (n: 42, 56%) and abnormal physical/neurological findings such as abnormal tone, hemiparesis, hemidystonia, microcephaly, dysmorphic facial features, neurocutaneous features, and autistic traits with or without dysmorphic features (n: 15, 20%). The results of MRI studies of 63 patients were available; 38 of them (60%) had abnormal findings (Table II).

Table I. Seizure Etiology of the Patients

Idiopathic	8 (12.6%)
Cryptogenic	16 (25.4%)
Symptomatic	39 (61.9%)
1. Hypoxic/infectious insults during perinatal period	15
2. Head trauma	7
3. Meningitis-encephalitis	5
4. Central nervous system malformation	4
5. Intracranial vessel abnormality/hemorrhage	4
6. Neurocutaneous disorder	3
7. Intrauterine infection	2
8. Chromosomal abnormality	1
9. Extracranial malignancy	1
10. Metabolic disorder	1
11. Others (febrile convulsion, history of vaccination, history of indirect hyperbilirubinemia as a newborn)	10

Seizure Types and Epilepsy Syndromes

Twenty-eight patients (37%) had primary generalized seizures, 42 patients (56%) had partial onset seizures with or without secondary generalization, and five patients (7%) had two or more types of seizures (Table III). Among 63 patients with MRI, 13% (n: 8) had idiopathic epileptic syndromes, 25% (n: 16) had cryptogenic epileptic syndromes, and 62% (n: 39) had symptomatic epileptic syndromes (Table I).

AED Treatment and Efficacy

Seventy-six percent of patients (n: 57) had been on polytherapy before LTG was added to the treatment. Only 7 patients (9.3%) were maintained on LTG monotherapy; 4 of them showed improved seizure control. The mean age at the introduction of LTG was 8.9±4.1

Table II. Cranial MRI Findings of the Patients Classified According to their Response to Lamotrigine Treatment

Cranial MRI Findings	Total (n=63)	No. of patients responsive to LTG (n=34)	No. of patients unresponsive to LTG (n=29)
1. Normal	25	14	11
2. Mesial temporal sclerosis	11	3	8
3. Cortical atrophy	5	2	3
4. Cortical dysplasia	4	2	2
5. Hydrocephalus	4	3	1
6. Intracranial vessel abnormality	3	2	1
7. Sequela of hypoxic ischemic injury	3	2	1
8. Intracranial hamartoma/tumor	3	3	0
9. Sequela of meningitis-encephalitis	2	1	1
10. Nonspecific white matter alterations	2	1	1
11. Sequela of intracranial hemorrhage	1	1	0

Table III. Efficacy of LTG in Patients with Partial and Generalized Seizures

Seizure Type	No. of patients responsive to LTG	No. of patients unresponsive to LTG	Total
Primary generalized seizure	15 (53.6%)	13 (46.4%)	28
Partial seizure with ± secondary generalization	24 (57.1%)	18 (42.9%)	42

years (range: 1-18.5 years, median: 9 years). The mean duration of epilepsy in patients was 8.6±5.6 years (range: 0-17.5 years, median: 8.5 years). The mean duration of the treatment with LTG either alone or in combination with other AEDs was 25.4±27.1 months (range: 3-120 months, median: 12 months). The mean dosage of LTG was 6.4±4.7 mg/kg/day (range: 1.5-20 mg/kg/day; only 2 patients on polytherapy received LTG at a dosage of 20 mg/kg/day, median: 5 mg/kg/day). The patient profile in the study group is shown in Table IV.

There was no statistically significant difference in the efficacy of LTG in seizure control between the patients with partial epilepsy and those with primary generalized epilepsy (p=0.961). LTG reduced seizure frequency by at least 50% in 57.1% of patients with partial seizures, and in 53.6% of patients with primary generalized seizures (Table IV). Four of 8 patients with idiopathic epileptic syndromes, 9 of 16 patients with cryptogenic epileptic syndromes, and 21 of 39 patients with symptomatic epileptic syndromes were responders. Nine of the responders (12%) had

Table IV. Patient Profile in the Study Group

Total	75
Male	46
Female	29
Age of introduction of LTG treatment	Mean: 8.9±4.1 years
Duration of LTG treatment	Mean: 25.4±27.1 months
Dosage of LTG	Mean: 6.4±4.7 mg/kg/day
Treatment status with LTG	
Monotherapy	7
Add-on	68

complete resolution of their seizures. There were no statistically significant differences between responders and nonresponders for age of seizure onset, duration of epilepsy, age of LTG introduction, dosage of LTG, or intelligence scores. There was a significant difference between responders and nonresponders for the duration of LTG treatment (p=0.011). The patients who achieved more versus less than 50% reduction in seizure frequency received LTG at a mean duration of 30.9±28.4 months (median: 20 months) versus 18.8±24.3 months (median: 10.5 months), respectively.

Side Effects

The side effect profile of LTG during the treatment is shown in Table V. The most common side effects included mild skin rashes and gait incoordination.

Table V. Side Effect Profile of LTG Observed During the Treatment of the Patients with Intractable Epilepsy

Side effects	Number of patients	No. of patients in whom LTG was discontinued due to side effects
Skin eruption, rash	4	1
Ataxia	2	–
Drowsiness	1	1
Dysarthria	1	–
Behavioral issues	1	–
Stomachache	1	–
Hirsutism	1	–

Discussion

Previous studies on LTG efficacy indicated that 40% of children who have partial onset seizures with or without secondary generalization achieve more than 50% reduction in seizure frequency[1-5,27,28]. Patients with frontal lobe epilepsy were found to be more responsive to LTG than those with temporal lobe epilepsy in a trial correlating localization of the epileptic focus with LTG efficacy[5]. For generalized epilepsies, especially absence, juvenile myoclonic seizures, and other seizure types associated with idiopathic generalized epilepsies and Lennox-Gastaut syndrome, LTG has high rates of seizure control[1-5,9-12]. In this study, a higher success rate of LTG therapy was found for both primary generalized epilepsy and partial epilepsy compared to that of previous studies. LTG reduced seizure frequency by at least 50% in 57.1% of patients with partial seizures, and in 53.6% of patients with primary generalized seizures. There was no statistically significant difference in the efficacy of LTG in seizure control between the patients with partial or primary generalized epilepsy. The least favorable outcomes were noted in patients with perinatal hypoxic ischemic damage, as observed in a previous study[28]. In a previous study comparing the efficacy of vigabatrin and LTG in treatment of childhood epileptic syndromes, LTG was found to be more effective for children with generalized epilepsies than those with partial epilepsies[5].

Most patients admitted to our EEG laboratory are on polytherapy and few are on monotherapy. Therefore, the study group does not reflect the general childhood epilepsy population. Mean seizure frequency in the three months preceding and following LTG treatment initiation was evaluated on the basis of seizure diaries kept by parents. We are limited by parents' reliance on the treatment and their tendency to exaggerate any improvement. Within these limitations, we observed a beneficial response in a considerable proportion of cases. Responders and nonresponders differed in duration of treatment, which was relatively long (mean: 25.4±27.1 months, median: 12 months, range: 3-120 months). Patients who achieved more than 50% reduction in seizure frequency received LTG for a longer period of time. This can be interpreted as longer treatment being more effective, or, conversely, more effective treatment being pursued longer. We examined this issue by comparing the degree of response at three and six months whenever data were available. The rate of responders did not vary between these two time points because certain patients whose seizures diminished after the initiation of LTG had recurrences in later months, as frequently observed in refractory

epilepsy, while many others showed partial response in the first few months and more pronounced response at six months. Conversely, if response was null or minimal at three months, it did not increase in later follow-up. This supports continuing LTG only if there is some reduction in seizures in the first three months of treatment. A significant sustained benefit with longer treatment was also reported in other, long-term studies[23,24].

The incidence of adverse events was relatively low (15%) in this study, with the most common being skin rash, which developed in four patients, but did not evolve into Stevens-Johnson syndrome. Neurological symptoms developed in five patients and included ataxia, drowsiness, dysarthria and behavioral problems. Medication was discontinued in two patients due to rash and drowsiness, respectively. As reported in previous studies, we suggest that LTG has a favorable side effect profile when administered as monotherapy or adjunctive therapy[22-24].

In conclusion, we recommend that LTG should be considered for intractable partial seizures and primary generalized epilepsies that fail to respond to other medications. We also suggest that if there is some response within the early months after initiation of treatment, LTG can be continued with doses adjusted individually for each patient. Side effects are rare but should be carefully monitored.

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