

Lamotrigine as an Add-on Therapy in Intractable Paediatric Epilepsy - The Kuala Lumpur Hospital Experience

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Summary

An observational study of all children with intractable epilepsy at the Paediatric Institute prescribed Lamotrigine as an add-on therapy between January 1994 and November 1998 was conducted. A total of 30 children were recruited. Three had adverse effects to the drug and it was withdrawn. Of the remaining 27, there were 20 boys and 7 girls, ranging from 2 to 17 years. Fifteen children had generalised epilepsy, 6 had partial epilepsy, 2 had West syndrome and 4 had Lennox Gastaut syndrome. Six children (20%) became seizure free, and 14 (54%) had a greater than 50% reduction in seizure frequency. However 7 children (23%) did not respond and 3 experienced a deterioration in seizure severity. Nine children were noted to have an improvement in alertness and behaviour. Our small series suggests that Lamotrigine is useful as add-on therapy in childhood intractable epilepsy.

Key Words: Lamotrigine, Childhood epilepsy

Introduction

The management of refractory epilepsies always poses a challenge to the clinician. Lamotrigine, a relatively new anti epileptic drug was initially used in Europe in 1991 and U.S.A. in 1994 for the adjunctive treatment of refractory partial seizures. Since then, numerous double-blind placebo-controlled trials carried out in adult patients have confirmed Lamotrigine's efficacy in the treatment of refractory partial¹⁻⁷ and generalized seizures^{8,9}.

In the paediatric population, open single blind and randomized control trials have shown promising benefits in the therapy of various types of seizures and epileptic syndrome^{1,10-15}.

Lamotrigine inhibits voltage sensitive sodium currents through preferential interaction with the slow inactivation of sodium channels suggesting that it may act selectively against high frequency epileptiform discharges. It also suppresses burst firing in cultured rat cortical neurons and sustained repetitive firing in the mammalian spinal cord while leaving neuronal synaptic conduction unaffected. Besides this, Lamotrigine modulates calcium conduction involved in the release of excitatory amino acid i.e. glutamate in the corticostriatal pathway^{1,16}.

Lamotrigine has been available for use in Paediatric Institute since 1994. We report here the benefits of Lamotrigine as add on therapy in our population of Malaysian children with intractable seizures.

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Materials and Methods

This study reviewed patients from January 1994 to October 1998. Lamotrigine was used as add-on therapy in patients with intractable seizures, defined as at least more than one seizure a week while being on two or more anti epileptic drugs. All the children who received lamotrigine as add on therapy had been tried on maximal tolerated doses of other anticonvulsants. Lamotrigine was introduced according to a recommended standard protocol. Patients who were on valproate were started on 0.15mg/kg/day of Lamotrigine initially, increasing every fortnightly to a maintenance of 1 - 5mg/kg/day. For those who were on liver enzyme inducing drugs such as phenobarbitone, phenytoin and carbamazepine, Lamotrigine was started at 0.6 mg/kg/day, increasing every 2 weeks to a maintenance dosage of 5 -15mg/kg/day¹.

The minimum follow-up period was 6 months after commencing Lamotrigine. Our patients had been diagnosed to have epilepsy for about 6 months to 10 years when Lamotrigine was added. All the patients had a well-documented detailed history, physical examination and appropriate investigations. Data that were collected in these patients included age of onset of seizures, types and frequency of seizures, identifiable etiology or syndrome, electroencephalographic findings, neurological and developmental assessment, age Lamotrigine was started, frequency of seizures before and after adding Lamotrigine, response to Lamotrigine, (100% control, more than 50% control, less than 50% control), time interval before response was obtained, dosages used, non seizure related benefits and adverse effects.

Results

A total of 30 patients had received lamotrigine as add on therapy. Three children developed a rash and the drug was stopped. These were excluded from further analysis. The remaining 27 children consisted of 20 boys and 7 girls giving a male: female ratio of 2.8:1. Only 4 had normal cognitive function and neurological examination at the start of Lamotrigine.

The age distribution of our patients (Figure 1) ranged from 2 1/2 to 14 years. The mean age was 9.0 years and median 8.6 years. Sixty percent of our patients were in the 4 to 6 years and 10 to 12 years age group.

Six children (22%) had partial seizures while the remaining 21 (78%) had generalized seizures. Of the 6 with partial seizures, 1 had complex partial seizures, 2 had simple partial seizures evolving to generalised seizures and 3 had complex partial seizures with secondary generalisation. Among the children with generalized convulsions, 2 had West syndrome and 4 had Lennox Gastaut Syndrome. The remaining 15 children had various combinations of generalised convulsions as shown in Table I. Most patients (17 or 63%) had more than seizure type with 1 patient having 4 different types of fits.

A definite underlying etiology was identified in 11 patients (Figure 2), the other 16 falling into the cryptogenic/idiopathic group. Twenty (74%)

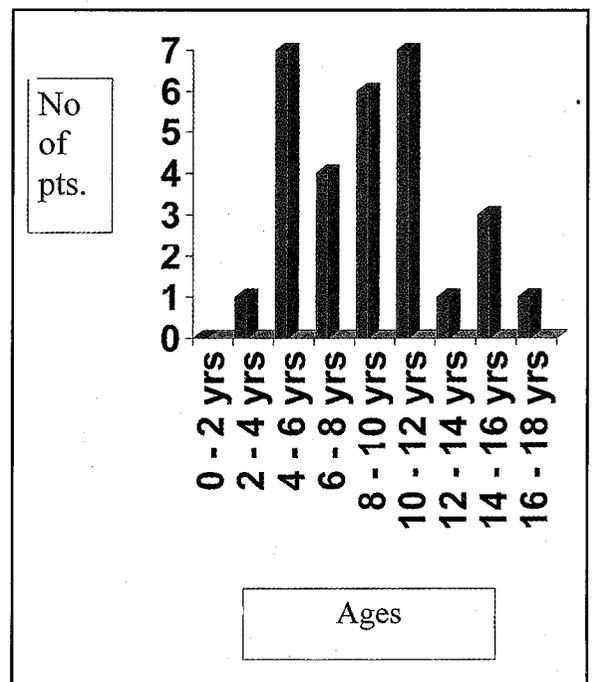


Fig. 1: Age distribution.

Table I
Types of Generalized Seizures

Types	No. of Patients
Abscences	2
Atypical absences	1
Myoclonic	9
Clonic	1
Tonic	3
Tonic - clonic	7
Atonic	4

Table II
Response to Lamotrigine

Types of Seizures	No. of Patients	Response		
		100%	>50%	<50%
*Partial	6	2	4	-
*Generalized	15	1	9	5
*West syndrome	2	2	-	-
*Lennox- Gastaut	4	1	1	2
Total	27	6	14	7

All our patients who became seizure free had no demonstrable etiology as a cause of their seizures. Lamotrigine was also successful in bringing about a >50% decrease in seizure frequency in 7 (64%) patients with a demonstrable etiology.

Lamotrigine achieved good control of seizures in 80% of our patients within 6 months of commencement, with 50% of patients responding within 3 months.

The drugs most frequently used in combination with Lamotrigine in those who responded favourably were sodium valproate in 10 (50%) patients, followed by the sodium valproate and clonazepam combination in 5 (25%). Other combinations used were with clonazepam alone (3 patients), carbamazepine and phenobarbitone (1 patient each). The dosages used ranged between 1mg - 5mg/kg/day. Thirteen patients (64%) required more than 3mg/kg/day to achieve control.

In addition to better seizure control, 9 (33%) of our patients subjectively reported positive non-seizure related benefits. Two children became more cheerful, 2 more alert, 2 had reduced hyperactivity and 3 were said to have a better interaction with the family resulting in a better quality of life. However, no formal psychometric testing was performed.

Six (22%) patients had adverse effects three patients developed a skin rash and Lamotrigine was withdrawn. In the remaining 3 patients with

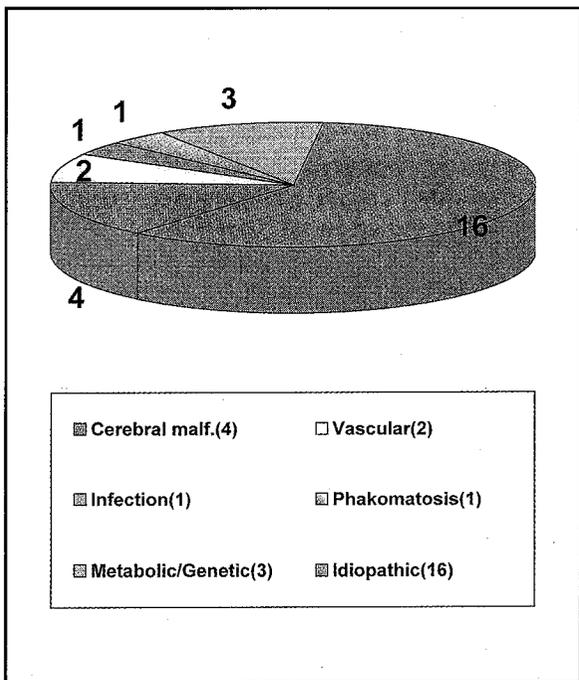


Fig. 2: Etiology of seizures.

of our patients responded favourably to Lamotrigine with 6 (22%) achieving complete seizure control. All our patients with partial seizures and 67% of patients with generalized seizures responded favourably.

adverse effects, a reduction in the Lamotrigine dose markedly reduced drowsiness and aggressive behavior in 2 patients. The third patient experienced drowsiness only during the early phase of Lamotrigine introduction. In addition 1 child was noted to have irritation of the eyes during the early part of treatment, but the actual causal relationship with Lamotrigine is uncertain.

Discussion

This was an observational study in our population of children with problematic, intractable epilepsies at our tertiary center.

Our results showed that Lamotrigine was effective in both the partial and generalized seizure types as all 6 (100%) and 10 (67%) patients from these groups respectively had more than 50% reduction in seizure frequency.

In other uncontrolled studies done overseas to assess the efficacy of Lamotrigine as add-on therapy in children and adolescents with refractory seizures of multiple types, it was shown that 40% of patients achieved more than 50% reduction of seizures and 10% had total control after 3 months of therapy¹. In a multicenter study involving 285 children below 13 years from 37 centers by Besag FMC *et al.*, it was shown that seizure frequency was reduced by 50% or more in a third of patients and Lamotrigine was effective in all seizure types examined¹⁰.

E. Schlumberger *et al.* found 11 out of 120 children (9%) had become seizure free while 34 (28%) had more than 50% reduction in seizure frequency at 3 months of therapy¹¹. A placebo-controlled trial of Lamotrigine as an add-on therapy for partial seizure involving 201 children from the United States and France proved Lamotrigine to be effective in reducing the frequency of partial and secondary generalized seizures with a 49% reduction in the treated group compared with 13% in the placebo group¹⁴.

In our study, we also found that Lamotrigine showed promising results in the syndromic epilepsies noted for their refractoriness to therapy. Two of our patients with West syndrome who had uncontrolled fits for a mean duration of 2 years before Lamotrigine was added became seizure free. Two out of 4 of our patients with Lennox-Gastaut syndrome responded with 1 becoming seizure free and the other achieving more than 50% reduction in seizure frequency.

Although our numbers are too small to draw definite conclusions regarding the use of Lamotrigine in West syndrome and Lennox-Gastaut syndrome, it is encouraging to note that other authors have also noted somewhat similar observations. E. Schlumberger *et al.* found that among 13 of his patients with West syndrome, 2 became seizure free and another 2 had more than 50% control of seizures. Three of his patients with Lennox-Gastaut syndrome became seizure free and another 3 had more than 50% of control of seizures¹¹. A landmark double-blind placebo-controlled study conducted by J. Motte *et al.* regarding Lamotrigine for generalized seizures associated with Lennox-Gastaut syndrome showed that 33% of patients in the Lamotrigine group demonstrated a reduction of at least 50% in the frequency of seizures compared to 16% of those in placebo group¹⁵.

Seven of our patients did not respond to Lamotrigine. Two of them had Lennox-Gastaut syndrome and the other 5 were from the generalized seizure group. Three of the 5 patients in the generalized seizure group had myoclonic seizures and drop attacks which worsened with addition of Lamotrigine. Other authors have also reported this phenomenon. Sander *et al.* noted 5 out of 7 of his adult patients with myoclonic epilepsy worsened with Lamotrigine¹⁷. Guerrini R *et al.* reported that there was pronounced seizure deterioration during Lamotrigine therapy that was not attributable to the disease process of severe myoclonic epilepsy¹⁸.

However, there were another 5 patients in our study with myoclonic seizures who responded with more than 50% control of seizure. To sum this controversy, Wallace SJ in his publication, concluded that the exact place of Lamotrigine, which controls some myoclonus and makes others worse, requires further study¹⁹.

Lamotrigine in our study also achieved good medical control of seizures in 7 out of 11 patients with symptomatic epilepsies, which are usually more difficult to control.

It is important to note that an adequate trial of Lamotrigine should be given as the majority of our patients only responded after about 3 - 6 months of treatment. Besag *et al.* also reported that 69% of his patients had improvement of seizures control at 12 weeks and 74% at 48 weeks of Lamotrigine treatment¹³.

Eighty three percent of our patients who became seizure free were on a combination of sodium valproate and Lamotrigine. Other authors have also noted a favourable response to this combination in head on head trials with other anticonvulsants, and have postulated some form of synergism between sodium valproate and Lamotrigine²⁰.

We found that Lamotrigine was generally well tolerated. Only 3 of our patients experienced adverse effects. Three patients experienced drowsiness and dosage reduction was enough to ameliorate the symptoms in 2 of them. Other

adverse effects reported with Lamotrigine therapy included headache, asthenia, rash, nausea and somnolence^{1,21}. Three patients of the original cohort of 30 developed a rash. This figure of 10 percent is comparable to other published reports¹. It has been suggested that the risk of rash maybe increased by co-administration of Lamotrigine with valproate, exceeding the recommended initial starting dose and dose escalation of Lamotrigine^{1,22}.

Lamotrigine's acclaimed positive psychotropic effect was observed in 9 of our patients. This non-seizure related benefits included a feeling of an improved quality of life, mood alertness and reduced hyperactivity. However, a more formal and objective assessment is warranted to validate these findings. P.Uvebrani *et al.* reported that 24 out of his 45 patients with intractable epilepsy had an improved mental state and longer attention span. He also found that there was a reduction in autistic symptoms in 8 out of 13 autistic children in his study¹².

In conclusion, as reported by Besag *et al.*¹³, we found that Lamotrigine was generally well tolerated, safe and effective in a wide spectrum of seizure types with a sustained and consistent efficacy throughout the whole of our study period.

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