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Lamotrigine Treatment in Childhood Drug-Resistant Epilepsy

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Abstract: Rationale: In this study the efficacy of Lamotrigine was evaluated in children with medically intractable epilepsy.

Methods: 22 epileptic children, ranging between 4.2 years and 15 years of age (mean 9.3 years) were included in this study. Twelve (54.5%) were male and 10 (45.5%) were female. The seizure types were classified according to the International League Against Epilepsy criteria: simple partial seizures (8 cases), infantile spasms (4 cases), generalized tonic-clonic seizures (2 cases), tonic seizures (2 cases), complex partial seizure (2 cases), typical absence seizures (2 cases), myoclonic astatic seizures (1 case) and atypical absence seizures (1 case). The neurological and physical examination, seizure frequency, seizure types, electroencephalograms, computed tomography and magnetic resonance imaging findings were evaluated in all cases. The cases were followed up for 5 to 39 months (mean 16.8 months). The response was evaluated as 100%, 75% and 50% reduction in seizure frequency.

Results: Response was favourable in 9 a total of cases (40.9%): 100% in 2 cases (9.1%), 75% in 4 cases (18.2%) and 50% in 3 cases (13.6%). Six cases developed tolerance. We had no response in 7 cases (31.8%). The seizure types were generalized tonic-clonic, absence and simple partial seizures in 6 cases in which we had 100% and 75% response.

Key Words: Lamotrigine, drug resistant epilepsy, intractable epilepsy

Introduction

Lamotrigine (LTG) (3,5-diamino-6-(2,3-dichlorophenyl-1,2,4-triazine) is an antiepileptic drug and its anticonvulsant action is due to inhibition of glutamate release by an action at voltage-sensitive sodium channels. Its chemical structure is different from antiepileptic drugs; it has a weak antifolate efficacy (1). It is been in use for intractable epilepsy in over 50 countries. It has a broad spectrum of anticonvulsant activity and can be used in multiple seizure types. Double-blind, placebo-controlled, add-on cross-over trials in 283 people with refractory epilepsy have shown efficacy against partial and generalized tonic-clonic seizures (2,3). It has complete bioavailability and a very long plasma elimination half-life (24+5.7 h). In animal models it has been shown to have an antiepileptic profile similar to phenytoin and carbamazepine and in controlled studies it has been shown to reduce partial and generalized tonic-clonic seizures (4). The best results are obtained in generalized epilepsies including absence epilepsy, Lennox-Gastaut syndrome (LGS) and other types of symptomatic generalized epilepsy. Its efficacy is not clear in myoclonic absence syndrome and cryptogenic myoclonic epilepsy. In this report we evaluated the efficacy of LTG as add-on therapy in intractable epilepsy.

Materials and Methods

Twenty-two patients, 10 girls and 12 boys with ages ranging from 4.2 years to 15 years (mean 9.3 years) entered the study. Age at epilepsy onset was mean 3.3 years (1.5 months to 11 years). The duration of epilepsy was mean 5.5 years (1.5 years to 15 years). In 10 cases, epileptic syndromes were idiopathic/ cryptogenic, and in the remaining 12 cases symptomatic.

The selection criteria were as follows:

- The diagnosis for epilepsy must be definite.
- Syndromes can be defined according to the International League Against Epilepsy (ILAE) classification.

- The patient must had have at least 2 seizures in the last 3 months.
- Seizures must be drug resistant (epilepsy is considered drug-resistant when there is no response to at least 2 major antiepileptics in appropriate dose, combination, administration and blood level).
- Patients with progressive disease were not included.

Patients had a screening history including antiepileptic drug history, physical and neurologic examination, laboratory tests (complete blood count, routine biochemistry), EEG, brain computed tomography (CT) and magnetic resonance imaging scan. Clinical details and seizure characteristics are given in Table 1. LTG was administered in a low dose, then the dose was increased stepwise twice weekly. The initial dose was 0.5 mg/kg/day and was increased to a maximum of 5 mg/kg/day in patients taking enzyme-inhibiting drugs such as VPA. In patients taking enzyme-inducing drugs such as carbamazepine, phenobarbital and phenytoin the initial dose was 2 mg/kg/day and was increased to a maximum of 15 mg/kg/day. We administered 10 mg/kg/day LTG to the patients who were receiving both enzyme-inducing and inhibiting drugs. The drugs and mean antiepileptic drugs count of all patients before and after lamotrigine was administered are given in Table 2. We examined the side effects and plasma concentrations of all antiepileptic drugs administered with LTG. We evaluated the seizure frequency before and after LTG therapy. The seizure frequency was registered for a period of 3 months before starting the LTG treatment. The mean seizure frequency was more than 10 daily in 3 cases, 1-10 daily in 12 cases, more than 4 in a month in 6 cases, 2-4 in a month in 1 case. Improvement was defined as a decrease in seizure frequency of 50% or more in the 3 months after starting LTG treatment. Tolerance was defined as a reduction in seizure control after >3 months of significant improvement. Worsening was defined as an increase in seizure frequency of more than 50%. Patients with results between these 2 limits were considered unchanged. Ten patients had mixed-type seizures. The seizure types were infantile spasm, simple partial seizures, complex partial seizures, generalized tonic-clonic seizures, tonic seizures, myoclonic astatic seizures, typical and atypical absence seizures. We determined the predominant seizure types due to seizure frequency and severity. Mental retardation was found in 11 cases, and focal neurologic abnormalities in 7 cases.

Results

We classified the cases into three groups according to their response to therapy. Group I included 7 cases (31.8%) considered totally unresponsive to the LTG treatment. Epilepsy was symptomatic in 4 of these patients. In group II, 6 cases (27.3%) developed tolerance. Four of them were considered symptomatic. Nine cases (40.9%) were classified in group III. In these cases long lasting response to LTG treatment was observed. Five of them were idiopathic or cryptogenic. Four of them were symptomatic. We evaluated the response of LTG treatment according to seizure types. LTG was effective in 2 cases with absence seizures. We observed 100% response in one case with simple partial seizures but only 3 of the 7 cases with secondary generalized simple partial seizures had 75% response to LTG. In infantile spasm, tonic, atypical absence and complex partial seizures, the response was a 50%

Table 1. Our 22 patients, clinical and seizure characteristics.

Female/Male	12/10
Mean age	9.3 years
Mean age for the onset of epilepsy	3.3 years
Mean duration of epilepsy	5.5 years
Patients, seizure frequency	
2-4 seizures/month	1
4 or above seizures /month	6
1-10 seizures/day	12
10 or above seizures/day	3

Table 2. The drugs and mean antiepileptic drugs count of all patients before and after lamotrigine was administered.

Drug	Before LTG (patient number)	After LTG (patient number)
Valproate	21	10
Carbamazepine	14	14
Phenytoin	2	1
Clonezepam	2	-
Phenobarbital	10	2
Ethosuccimide	3	-
Adreno corticotropic hormone	7	-
Mean anti-epileptic drugs count	2.6 drug	1.2 drug

decrease in seizure frequency. Four of the 10 cases with generalized tonic-clonic seizures had a 75% or greater response to LTG. Seizure types, etiology and response to the lamotrigine treatment of our patients are given in Table 3. We had no response in myoclonic astatic seizures. We recorded an improvement in behaviour, alertness and mental state in 5 (22.7%) cases subjectively. In 4 of them the seizures were also controlled. The other case was Rett syndrome. The seizures continued in this case but improvement of behaviour and mobility was observed. The adverse effects were present in 2 cases (9%). Ataxia, sedation and vomiting were observed in a patient in group II when the dose of LTG increased. In the other case, taking LTG and valproic acid together, ataxia and vomiting disappeared by decreasing the dose of valproic acid.

Discussion

LTG is a relatively promising new drug for epilepsy. In a multicentre study of 285 cases, Besag et al. obtained a 50% or more reduction in 1/3 of the intractable epilepsy cases. They found LTG was well tolerated and effective for a broad range of seizure types, especially in typical and atypical absence seizures (5). We had a 50% decrease in seizure frequency in atypical absence seizures. The response was 100% in a patient with absence seizures. The same group evaluated the long-term safety, tolerability and effect of LTG on seizure control in epileptic pediatric patients. One hundred and fifty-five children with intractable epilepsy received add-on or monotherapy LTG for up to 4 years. Thirty-four patients received LTG monotherapy. Their assessment of seizure control compared with the 3-month period before

Table 3. Seizure types, etiology and response to the lamotrigine treatment of our 22 patients by groups according to response to the lamotrigine treatment. Group I: totally unresponsive to the treatment, Group II: Lamotrigine treated with developed tolerance, Group III: responsive to the treatment. The predominant seizure types were described firstly in seizure types column.

	Patient No:	Seizure Types	Etiology	Results
Group I	1	tonic	cerebral hemorrhage	---
	4	secondary generalized SPS	idiopathic/cryptogenic	---
	5	secondary generalized SPS	idiopathic/cryptogenic	---
	6	CPS, GTC	Rett syndrome	---
	8	myoclonic astatic , GTC	idiopathic/cryptogenic	---
	18	secondary generalized CPS, GTC	cerebral hemorrhage	---
	19	tonic	cerebral malformation	---
Group II	9	Atypical absence, GTC	idiopathic/cryptogenic	50%
	12	IS, Tonic, GTC, CPS	cortical malformation	50%
	13	IS, GTC, Tonic	hypoxic ischemic encephalopathy	50%
	15	secondary generalized SPS	idiopathic/cryptogenic	50%
	17	secondary generalized SPS	delay in myelinization	50%
	21	IS, Secondary generalized CPS	cerebral malformation	50%
Group III	2	GTC	delay in myelinization	75%
	3	secondary generalized SPS	idiopathic/cryptogenic	75%
	7	absence seizures	idiopathic/cryptogenic	100%
	10	IS, Tonic	hypoxic ischemic encephalopathy	50%
	11	GTC	idiopathic/cryptogenic	50%
	14	secondary generalized SPS, GTC	hypoxic ischemic encephalopathy	50%
	16	SPS, GTC	idiopathic/cryptogenic	100%
	20	absence seizures	idiopathic/cryptogenic	75%
	22	secondary generalized SPS	hypoxic ischemic encephalopathy	75%

SPS: simple partial seizure, CPS: complex partial seizure, GTC: generalized tonic-clonic, IS: infantile spasm

LTG treatment, indicated that seizure control was generally maintained during long-term LTG treatment for up to 4 years. For 19 patients improvement in behaviour, alertness and seizure severity were recorded subjectively, sometimes independent of seizure control (6). Oller et al. achieved complete seizure control in 38% of LGS cases (n:13) with LTG at doses of 100-400 mg/day (7). Motte et al. and Eriksson et al. also reported that LTG was an effective and well-tolerated treatment for seizures associated with LGS (8,9). Timmings et al. administered LTG add-on therapy in the treatment 11 patients with LGS syndrome. Ten cases experienced over 50% reduction in seizure frequency. One case experienced no change in seizure frequency. No side effects were reported (10). Donaldson et al. analyzed data from 16 LGS patients. Fifty-three percent (8 of 15) had a >50% reduction in seizure frequency with LTG therapy. Tonic, atonic, generalized tonic-clonic and atypical absence seizure frequency but not myoclonic seizure frequency decreased significantly during LTG therapy (11). In our study we also had no response in myoclonic astatic seizures. Belanger et al. administered Vigabatrin and LTG in 105 cases and found this combination more effective in frontal lobe epilepsy than temporal lobe epilepsy. They also achieved success in treatment of generalized epilepsy in their retrospective study (12). Farrell et al. evaluated the efficacy and adverse effects of LTG in an open, prospective study of 56 children with generalized epilepsy. Six children (11%) became seizure-free, 24 (43%) had greater than 50% reduction in seizure frequency. Three of 15 patients with LGS achieved complete seizure control and eight demonstrated 50 to 90% improvements in seizure control. This study suggested that LTG may be a useful drug in the treatment of generalized epilepsies in children and should be considered earlier in the treatment of LGS (13). In the present study, LTG reduced spasms in only 1 of 5 children with West syndrome. In another open study of LTG treatment in children with infantile spasms, 5 of 30 were seizure-free at 3 months and the other 4 patients demonstrated greater than 50% reduction in seizure frequency (14). We had a 50% reduction in seizure frequency in our cases with infantile spasms. The most common adverse effects of LTG are rash, increase in seizures, anorexia, lethargy, vomiting, headache and deterioration in behaviour. Rashes are the most common adverse effect of LTG leading to discontinuation of therapy in the literature (5,13,15). It was reported that rashes were more common in patients who had a higher initial LTG dose and in patients receiving Valproic acid comedication (5,16). Belanger et al. reported rashes in only 2 of 105 patients receiving LTG (12). Eriksson et al. did not observe rashes, but they reported diplopia (n:3) and agitation (n:4) in their study with 30 patients (9). Increase in seizures was also reported in 13% and 14% of patients in 2 different studies (6,13). We did not observe rashes in our patients during LTG therapy. Ataxia, sedation and vomiting were observed in 2 of our cases. As a result, in our study 9 patients (41%) responded to LTG treatment. Six patients (27%) responded initially then developed tolerance, and the remaining 7 patients (32%) had no response. The therapy was successful especially in absence, partial and generalized tonic-clonic seizures. We observed a low number of side effects consisting of ataxia, sedation and vomiting in only 2 patients. Our conclusion is that LTG is well tolerated during long-term therapy and produces a good clinical response in children with intractable generalized epilepsy.

References

1. Ramsay RE: Advances in pharmacotherapy of epilepsy. Epilepsia 34:9-16,1993.
2. Binnie CD, Van Em de Boas W, Kasteleijn-Nolste-Trenite DG. Acute effects of Lamotrigine (BW 430c) in persons with epilepsy. Epilepsia 27:248-54,1986.
3. Risner ME for Lamictal Study Group. Multicenter, double-blind placebo-controlled, add-on crossover study of Lamotrigine (Lamictal) in epileptic outpatients with partial seizures. Epilepsia 31:619-20,1990.
4. Miller AA, Wheatley P, Sowyer DA, Baxter MG, Roth B. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug. Anticonvulsant profile in mice and rats. Epilepsia 27:483-9,1986.
5. Besag FM, Wallace SJ, Dulac CO. Lamotrigine for the treatment of epilepsy in childhood. J Pediatr 127:991-7,1995.
6. Besag FM, Dulac O, Alving J, Mullens EL. Longterm safety and efficacy of lamotrigine in pediatric patients with epilepsy. Seizure 6:51-6,1997.
7. Oller LF, Russi A, Oller Daurella L. Lamotrigine in Lennox-Gastaut syndrome. Epilepsia 32:58-9,1991.

8. Motte J, Trevathan E, Arvidsson JF, Barrera MN, Mullens EL, Manasco P. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. N Engl J Med 337:1807-13,1997.

9. Eriksson AS, Nergardh A, Hoppu K. The efficacy of Lamotrigine in children and adolescents with refractory generalized epilepsy: a randomized, double-blind, crossover study. Epilepsia 39:495-501,1998.

10. Timmings PL, Richens A. Lamotrigine as add-on drug in the management of Lennox-Gastaut syndrome. Eur Neurol 32:305-7,1992.

11. Donaldson JA, Glauser TA, Olberding LS. Lamotrigine adjunctive therapy in childhood Epileptic Encephalopathy (the Lennox-Gastaut syndrome). Epilepsia 38:68-73,1997.

12. Bélanger S, Coulombe G, Carmant L. Role of Vigabatrin and Lamotrigine in treatment of childhood epileptic syndromes. Epilepsia 39:878-83,1998.

13. Farrell K, Connolly MB, Munn R, Peng S, MacWilliam LM. Prospective, open-label, add-on study of Lamotrigine in 56 children with intractable generalized epilepsies. Pediatr Neurol 16:201-5,1997.

14. Veggiotti P, Cieuta C, Rey E, Dulac O. Lamotrigine in infantile spasms. Lancet 344:1375-6,1994.

15. Mackay FT, Wilton LV, Pearce GL, Freemastle SN, Mann RP. Safety of Long-Term Lamotrigine in epilepsy. Epilepsia 38:881-6,1997.

16. Richens A. Safety of lamotrigine. Epilepsia 35;37-40,1994.