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## A Randomized Open-Label Comparison of Lamotrigine and Valproate in Patients with Juvenile Myoclonic Epilepsy

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**Abstract:** The aim of this study was to evaluate the efficacy and tolerability of lamotrigine and valproate in patients with different types of generalized epilepsy characterized by myoclonic seizures as well as compare the efficacy of those two drugs. A pilot, randomized controlled trial analysis of 46 female patients (age 8-30 years) in a large university hospital. All patients underwent several interictal EEG including routine awake and sleep EEGs. Lamotrigine was started at the dose of 500 mg day<sup>-1</sup> and was progressively increased to a mean dose of 1500-2000 mg day<sup>-1</sup> in a time course of 8 weeks. The target maintenance dose for valproate was 800 mg day<sup>-1</sup> after starting valproate at the dose of 200 mg/12 h. The mean dose was reached within 4 weeks. Out of total 46 patients, 46 (100%) had juvenile myoclonic epilepsy; 43 (93.48%) had tonic-clonic; 5 (11%) had myoclonic absences. In the valproate and lamotrigine groups, there was significant reduction ( $p < 0.001$ ,  $p < 0.001$ ) in myoclonic seizure and tonic-clonic seizure frequencies. There was no clinically significant difference ( $p > 0.05$ ) between the effect of those two drugs that means the lamotrigine and valproate have similar effect in reducing the myoclonic seizure and tonic-clonic seizure frequencies. There was statistically significant effect ( $p < 0.05$ ) of those two drugs that means the lamotrigine and valproate also have significant effect in reducing the absences seizure frequency. The results suggest that lamotrigine monotherapy is a possible alternative for valproate among patients with juvenile myoclonic epilepsy who experienced unaccepted side effects or inadequate seizure control with valproate monotherapy.

**Key words:** Juvenile myoclonic epilepsy, lamotrigine, valproate

### INTRODUCTION

Epilepsy is actually a group of disorders sharing the occurrence of unprovoked seizures. It is a worldwide common chronic neurological disorder and one of the most common neurological disorders (Banerjee *et al.*, 2009; Cetinkaya *et al.*, 2008). Generalized epilepsies may be idiopathic with a good prognosis and include the syndromes of childhood absence, juvenile absence and juvenile myoclonic epilepsy (Valentin *et al.*, 2007). Juvenile myoclonic epilepsy is said to represent 5-11% of all epilepsy cases (Jallon and Latour, 2005). Its incidence has been estimated at approximately 1 per 100,000 populations, while its prevalence varies from 10 to 20 per 100,000. Juvenile myoclonic epilepsy makes its clinical appearance between 6 and 22 years of age, but 50% of cases present at ages 13-16 years. Myoclonic seizures are present in all patients (appearing at 12-18 years) and are associated with generalized tonic-clonic seizures in

80-97%, the average age of onset the latter being 16-18 years and with absence seizures in 12-54% of patients (Mehndiratta and Aggarwal, 2002).

Juvenile myoclonic epilepsy affects both male and female patients equally, although a female predominance has been described. Early onset of absence seizures is more common in girls, while boys present with them at a later age and in boys there is a predominance of asymptomatic absence seizures, that is, a typical electroencephalography (EEG) not accompanied by symptoms. A family history of epilepsy was present in 65.9% of 41 studied families and 36% had at least two family members affected by juvenile myoclonic epilepsy (Alfradique and Vasconcelos, 2007). Neurological drugs such as lamotrigine and valproate have a wide spectrum of efficacy against all seizure-types (Choi and Morrell, 2003; Perucca, 2002; Neels *et al.*, 2004). Lamotrigine is an effective and generally well tolerated broad-spectrum agent for adjunctive treatment of refractory seizures in

children, most notably in those with Lennox-Gastaut syndrome (Choi and Morrell, 2003; Trevathan *et al.*, 2006; Culy and Goa, 2000; Pina-Garza *et al.*, 2008). Controlled trials in the epilepsies expanded to study valproate effects on partial-onset seizures and on epileptic drop attacks (tonic and atonic seizures) (Peterson and Naunton, 2005; Koristkova *et al.*, 2006; Stefan and Feuerstein, 2007; Stephen, 2003).

However, few reports in controlled comparative studies between lamotrigine and valproate are available (Vrie-Hoekstra *et al.*, 2008; Kilaru and Bergqvist, 2007). Open studies suggest that although lamotrigine is effective and well tolerated in various idiopathic generalized epilepsy syndromes, there may be differences of efficacy in individual syndromes and seizure types (Valencia *et al.*, 2009). In this study, we aimed to evaluate the efficacy and tolerability of lamotrigine and valproate in patients with different types of generalized epilepsy characterized by myoclonic seizures as well as compare the efficacy of those two drugs.

## MATERIALS AND METHODS

We recruited patients diagnosed of generalized epilepsy who visited the Golestan Hospital, Ahwaz Jondishapour University of Medical Sciences for an open study from 2007 to 2008. The study group consisted of 46 female patients (age 8-30 years). The study was approved by the University Hospital and Ahwaz Jondishapour University of Medical Sciences Ethics Committees and all subjects and their guardians in case of children, granted informed consent to participate. In all patients the diagnosis of generalized epilepsy was based on the published Classification of Epilepsies (Tuxhorn and Kotagal, 2008; Engel, 2006). All clinical records were analyzed. The following clinical characteristics were noted: sex, age, age of epilepsy onset, frequency of seizures, abnormal neurological examination, AEDs (Antiepileptic Drugs) used prior to lamotrigine and valproate, family history of epilepsy, laboratory findings. Seizure types were identified according to the classification of epileptic seizures and syndromes (Tuxhorn and Kotagal, 2008; Engel, 2006). All patients underwent several interictal EEG including routine awake and sleep EEGs. Some of the patients had a clinical MRI (1.5T) examination done, based on a protocol routinely used for patients with epilepsy, including T2-weighted images and a coronal 3D sequence with contiguous slices, with and without administration of gadolinium.

Lamotrigine was started at the dose of 500 mg day<sup>-1</sup> and was progressively increased to a mean dose of 1500-2000 mg day<sup>-1</sup> in a time course of 8 weeks. The

target maintenance dose for valproate was 800 mg day<sup>-1</sup> after starting valproate at the dose of 200 mg/12 h. The mean dose was reached within 4 weeks. Patients were clinically observed every 3 months. First of all we observed the side effects and tolerability of lamotrigine and valproate. Secondly, the efficacy was assessed by measuring changes in seizure frequency, especially myoclonic jerks. The basis for comparison was defined as the myoclonic seizure frequency in the 6 months prior to the commencement of treatment. We classified patients post-treatment into three categories: those achieving seizure freedoms, those achieving between 50 and 99% reduction in seizures and those with worsening. We observed the reduction of massive or focal epileptic myoclonus and other generalized seizures (e.g., absence, tonic-clonic).

Questionnaires assessing drug-related systemic toxicity and neurotoxicity were adapted from those used in the VA Cooperative Study (Cramer *et al.*, 1983), to reflect adverse effects commonly associated with valproate and lamotrigine treatment. The questionnaires were completed at each post-baseline visit (4, 8, 14 and 28 weeks).

**Statistical analysis:** To assess changes over time, the mean of valproate and Lamotrigine concentration ratios and 95% CIs were calculated per treatment groups. Categorical data were expressed as percentages and quantitative data as Mean, Standard Deviation (SD) and Range. Categorical variables were compared with Student's t-test. Log-transformed valproate and lamotrigine concentrations were compared by a repeated measures Analysis of Variance (ANOVA) using a model incorporating treatment groups (before and after treatment). Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed with the SPSS statistical software package (SPSS for Windows, v.13; SPSS, Inc., Chicago, IL).

## RESULTS

At study entry, 3 of 23 (13%) in the group assigned to lamotrigine and 3 of 23 (13%) of those assigned to valproate were excluded. All patients were converted to lamotrigine or valproate monotherapy. Overall, 17 of 19 (89.4%) lamotrigine-treated and 17 of 19 (89.4%) valproate-treated patients completed 28 weeks of treatment. Out of total 46 patients, 46 (100%) had juvenile myoclonic epilepsy; 43 (93.48%) had tonic-clonic; 5 (11%) had myoclonic absences. In the valproate group, there was significant reduction ( $p < 0.001$ ) in myoclonic seizure frequency. Lamotrigine group also have experienced a clinically significantly reduction ( $p < 0.001$ ) in myoclonic

Table 1: Comparing intra and between groups clinically significant effects of valproate and lamotrigine

Seizure reduction								
Valproate					Lamotrigine			
Seizure type	No.	Before ------(Mean ± SD)-----	After	p-value*	No.	Before ------(Mean ± SD)-----	After	p-value p-value**
Juvenile myoclonic	20	5.10±1.51	0.60±1.31	<0.001	22	4.77±1.63	0.86±1.69	<0.001 >0.05
Tonic-clonic	19	2.26±1.09	0.36±0.68	<0.001	20	2.3±1.26	0.45±0.94	<0.001 >0.05
Absences	3	5.00±0.81	0.66±0.45	CND	2	7.0±1.0	1.50±1.04	CND >0.05

\*Statistical comparison intra groups before and after valproate and lamotrigine treatment. \*\* Between groups differences; CND: Can not detected

Table 2: Most common adverse events (occurring in two or more patients) during randomized treatment

Adverse events	Lamotrigine (N = 23)		Valproate (N = 23)	
	No.	Percentage	No.	Percentage
Headache	4	17	2	9
Dizziness	2	9	2	9
Rash	3	13	0	0
Somnolence	2	9	0	0
Nervousness	1	4	0	0
Diplopia	2	9	0	0
Tremor	1	4	4	1
Myalgia	1	4	0	0
Anxiety	1	4	0	0
Weight gain	0	0	6	26
Hair loss	0	0	3	13
Dyspepsia	0	0	5	21
Menstrual irregularity	0	0	3	13
fatigue	0	0	4	17

seizure frequency (Table 1). There was no clinically significant difference ( $p>0.05$ ) between the effect of those two drugs that means the Lamotrigine and valproate have similar effect in reducing the myoclonic seizure frequency (Table 2). Twenty-two valproate-treated patients (95.6%) show tonic-clonic seizure. This patients had significant reduction ( $p<0.001$ ) in tonic-clonic seizure frequency.

Twenty-one lamotrigine-treated patients (91.3%) had tonic-clonic seizure which experienced a clinically significantly reduction ( $p<0.001$ ) in seizure frequency (Table 1). Also, there was no clinically significant difference ( $p>0.05$ ) between the effect of those two drugs on the myoclonic seizure frequency that means the Lamotrigine and valproate have similar effect (Table 1). Three of twenty three (13.04%) in the valproate group and 2 of 23 (8.69%) of those assigned to lamotrigine showed myoclonic absences seizure. There was statistically significant effect ( $p>0.05$ ) of those two drugs that means the lamotrigine and valproate have significant effect in reducing the absences seizure frequency (Table 1).

The most common adverse events are reported in Table 2. In detail, the lamotrigine-treated patients with treatment-limiting adverse events, four patients reported headache, three reported rash, two had Somnolence and two reported dizziness; the other Patients reported nervousness, tremor, anxiety and myalgia. Six

valproate-treated patients reported weight gain; five had dyspepsia, nausea, four reported fatigue and four showed tremor; the other patients reported headache, dizziness, hair loss and menstrual irregularity.

## DISCUSSION

From controlled studies we can obtain important data concerning effect and tolerability of anticonvulsant drugs. An attempt to compare different add-on therapies in refractory patients, that is, new anticonvulsants and vagus nerve stimulation, was made by Cramer *et al.* (2001). For the evaluation of the efficacy and tolerability of new anticonvulsants in new onset or pharmacoresistant epilepsies, practice parameters were also deduced from results of evidence-based assessments (French *et al.*, 2004). From the currently available evidence based on assessed data one can conclude that lamotrigine was found to be appropriate for adjunctive treatment of refractory partial seizures in adults. Limited evidence suggests that lamotrigine is effective for adjunctive treatment of idiopathic generalized epilepsy in adults and children as well as treatment of the Lennox-Gastaut-syndrome (Stefan and Feuerstein, 2007). This exploratory study suggests that, when titrated to response, moderate dosages of valproate and Lamotrigine may be similarly effective in juvenile myoclonic epilepsy in terms of patient's seizure-free during the 12 week maintenance period. However, lamotrigine and valproate had qualitatively different side effect profiles. At doses providing similar therapeutic effects, valproate had a higher side effect burden as measured with systemic toxicity scales. This study illustrates the challenges of conducting randomized, controlled trials in juvenile myoclonic epilepsy. Efficacy assessments were based on seizure data recorded by patients/families and were analyzed as reductions from baseline seizure frequency.

However, there have been many open case studies conducted with valproate in juvenile myoclonic epilepsy management. The open series that have been published using valproate show a 41-88% seizure-free rate for

patients receiving valproate, either as an add-on medication or as monotherapy (Atakli *et al.*, 1998; Kleveland and Engelsen, 1998). Case studies have also shown that a low, once-daily dose (500 mg) of VPA can effectively control juvenile myoclonic epilepsy and keep patients seizure free for as long as 2 years (Panagariya *et al.*, 2001; Karlovassitou-Koriari *et al.*, 2002). New studies that examined the efficacy of lamotrigine and valproate in juvenile myoclonic epilepsy have all shown that valproate has the best efficacy of the three (Prasad *et al.*, 2003; Nicolson *et al.*, 2004; Mohanraj and Brodie, 2005).

The incidence of adverse events reported during the valproate and lamotrigine monotherapy was consistent with that reported in other studies (Faught *et al.*, 2004; Saetre *et al.*, 2007). The most common drug-related adverse events in valproate-treated group included weight gain, nausea and fatigue and in the lamotrigine-treated patients were headache, rash, Somnolence and dizziness. As the combination of lamotrigine and valproate can increase the risk of serious rash (Faught *et al.*, 2004), the incidence of rash in this study was of particular interest. The incidence of drug-related nonserious rash (13%) is consistent with that reported in other studies of lamotrigine monotherapy (12%) (Faught *et al.*, 2004). Lamotrigine previously has been shown to be effective and well tolerated as monotherapy for epilepsy in patients switching from monotherapy with carbamazepine or phenytoin (Panayiotopoulos, 2000).

An anticonvulsant drug of the first generation such as valproate has an increased potential for interactions and side effects due to enzyme induction and/or inhibition. In addition to impairment of cognitive or endocrine functions, long-term use can give rise to changes in bone (osteoporosis) and connective tissue (gingival hyperplasia, Dupuytren's contraction, hypertrichosis, etc.) or hormonal-metabolic disturbances leading to sexual dysfunction (Herzog *et al.*, 2003; Pack *et al.*, 2003).

Coppola *et al.* (2004) evaluated the efficacy of lamotrigine in monotherapy as a treatment of absence seizures and showed 100% seizure control obtained in 55% patients and more than 50% seizures' decrease was observed in 25% of patients. Another study by Holmes *et al.* (2008) in patients with childhood absence epilepsy and juvenile absence epilepsy showed a seizure-free rate of 71%. Present results are not similar to those two researches confirming the efficacy of lamotrigine in myoclonic seizure and tonic-clonic epilepsy.

Although, lamotrigine and valproate are commonly used to treat children and adolescents with absence seizures, Posner *et al.* (2005) have some evidence from one trial that lamotrigine has an effect on seizures, but the trial was not designed to reflect or inform clinical practice. They also showed that compared lamotrigine and valproate head-to-head has insufficient power to show difference in efficacy of these drugs. Present results are similar Posner *et al.* (2005) confirming the lack of efficacy in lamotrigine and valproate on absences epilepsy.

In adults and adolescents, lamotrigine had been efficacious in focal and generalized seizures and its efficacy was similar or better than valproate and carbamazepine in several studies (Gamble *et al.*, 2006; Karceski *et al.*, 2005; Steinhoff *et al.*, 2005). In a retrospective study, Prasad *et al.* (2003) analyzed 22 consecutive juvenile myoclonic epilepsy adolescents treated with lamotrigine and valproate. They showed that seizure outcome did not differ when patients were receiving valproate monotherapy, compared to those receiving lamotrigine monotherapy. In agreement of this study our result also showed that lamotrigine was effective alternative options to valproate in the treatment of juvenile myoclonic epilepsy. Auvin (2008) study on drug treatment of juvenile myoclonic epilepsy claimed that lamotrigine should be preferred regarding teratogenicity and side effects of valproate. Maiga *et al.* (2006) reported a case of 19-year-old man with juvenile myoclonic epilepsy in whom lamotrigine lead to the exacerbation of generalized tonico-clonic seizures, reversible when lamotrigine was stopped and substituted by valproate.

While, dosing guidelines for conversion from monotherapy to lamotrigine monotherapy are established (Choi and Morrell, 2003), the use of lamotrigine monotherapy in patients converting from valproate monotherapy has to date been hampered by a lack of information on dosing strategies for conversion. This study addresses this issue by demonstrating that lamotrigine have been shown to be effective as monotherapy for conversion from valproate monotherapy to lamotrigine monotherapy.

In conclusion, both drugs were efficient in reducing the seizure monthly frequency, but there was no significant difference between them. The results of this study suggest that lamotrigine monotherapy is a possible alternative for valproate among patients with juvenile myoclonic epilepsy who experienced unaccepted side effects or inadequate seizure control with valproate monotherapy. Lamotrigine is a good alternative choice as first-line monotherapy in children and adolescents with different types of epilepsy and epilepsy syndromes.

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