RESEARCH ARTICLE

EFFECT OF LAMOTRIGINE ON PROPHYLAXIS OF PEDIATRIC CLASSIC MIGRAINE

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Received : 20-01-2009,
Last revised: 04-05-09,
Accepted: 23-06-09

Abstract

Objective

This study was conducted to evaluate the preventive effect of lamotringine on migraine aura and migraine attacks in children, afflicted with classic migraine.

Material & Methods

Conducted between October 2005 and April 2008 in the neurology clinic of Kashani hospital, Shahrekord, this study was a clinical trial, aimed at evaluating the prophylactic effects of Lamotringine administered to 21 children suffering from migraine with aura.

Results

Of the subjects, 52.4% of patients were female. The most common type of aura was visual (42.9%). Following use of Lamotrigine, significant reductions were seen in the frequency (from 5 ± 0.83 to 3.04 ± 1.65) and in intensity (from 6. 33 ± 1.08 to 3.66 ± 1.1) of migraine aura (P= 0.002). After 6 months of drug usage 66.6% of patients were improved.

Conclusion

Lamotringine is effective in reducing the migraine aura and intensity of attacks in patients suffering from migraine with aura, and is hence beneficial for prophylactic therapy in children with classic migraine.

Keywords: Lamotringine, Migraine aura, Classic migraine, children, prophylaxis

Introduction

Migraine is one of the most chronic common neurological disorders, afflicting more females (13-18%) than males (4.6 %) (1).

The prevalence of migraine has been reported to be 4% in children aged 7-14 years, in Sweden (2), 2.7 % at age seven and 10.6 % at fourteen, in Finland (3). Migraine is with or without aura with the ratio of one to five (1-4). In comparison to adults, the attacks in children are generally shorter in duration and frequency. One study reported the duration of migraine headaches in 61% of children to be less than five hours, with only 17% of children experiencing headaches early morning (3). Nausea and vomiting, other than headaches, are the main features of migraine in children, which have been reported in 81% of 7 year old patients (4).

Of the various theories regarding the pathogenesis of migraine or migraine aura, one of the most important is cortical spreading depression (CSD), a phenomenon usually associated with elevation of central nervous system hydrogen and potassium

ion, with the release of glutamate and nitrous oxide as excitatory neurotransmitters (2). The term CSD is used to describe a depression of spontaneous EEG and other cortical activities spreading across the cerebral cortex due to activity of noxious stimuli (5). The glutamate system is also described as a possible mechanism leading to neuronal hyperexcitability and CSD (6). Glutamate is increased in both forms of migraine, more markedly in migraine with aura (7). Also recent experiments have demonstrated that CSD depends on activation of a subtype glutamate receptor (8, 9).

Abnormal release of glutamate usually triggers an aura and migraine attacks, and the agents that inhibit glutamate release may be useful for prophylactic therapy in migraine with aura (9, 10). Lamotrigine, as an antiepileptic drug, inhibits sodium (Na) channels and also reduces glutamate release (10-13). In this regard, lamotrigine, as an inhibitory neurotransmitter (14, 15) has been shown to be effective in adult migraine attacks (14, 16, 17). This clinical study aimed to evaluate the preventive effect of lamotrigine on children between the ages of 4 - 14 years, with migraine headache. Duration of headaches, type of aura, common clinical symptoms, and the effects of sex and age on migraine headaches were also evaluated in this study.

Materials & Methods

This clinical trial, conducted between October 2005 and April 2008, in neurology clinic of Kashani hospital in Shahrekord, Iran, investigated a group of 21 pediatric patients, suffering from migraine with aura. Patients aged between 4 – 14 years of age were eligible if they were currently suffering from classic migraine with at least 2 attacks per month. Diagnosis was based on the International Headache Society (IHS) criteria and neurological examinations. Electroencephalography (EEG) and brain computed tomography scan (CT) were also obtained, when necessary (15). Patients with previous consumption of lamotringine (during 3 months before trial), hepatic and cardiac problems, or hypersensitivity were excluded from the study. Twenty-one patients with classic migraine eligible for this study were enrolled.

Type of aura, frequency and intensity of headaches were recorded for a period of 2 months prior to initiation of drug usage, and patients were followed up for 6 months.

Primary dose of lamotringine was 0.5 mg/kg/day and patients were evaluated monthly; intensity of headache was recorded for each migraine attack for 2 months before drug usage and 6 months following lamotrigine administration, on a scale of 0 to 10, with 0 = none, 1-3= mild, 4-7 = moderate, and 8-10 = severe. In this study improvement was considered as 50% reduction in the frequency of attacks and reduction of intensity to none or mild. Lamotrigine doses for patients not responding to initial drug doses were increased gradually (up to 3mg/kg/day) until their frequency and intensity of attacks decreased to the above mentioned levels; these doses were then continued until the end of the experiments. Data were analyzed by SPSS 16 using non parametric tests (Wilcoxon rank test, Chi square and Mann-Whitney U test). $P< 0.05$ was considered as significant.

Results

The patients mean age was 8.9 ± 1.94 (range 4 to 12 y); 52.4% were female. Results of the Wilcoxon rank test showed significant difference between both frequency ($P= 0.002$) and intensity ($P=0.002$) of migraine before and after treatment (table 1).

Table 1: Lamotrigine effects on migraine attacks (n=21).

Migraine attacks \ Quantity		Mean±SD	Range	P.value
Frequency	After	5±0.83	(4-6)	0.002
	Before	3.04+1.6	(1-6)	
Intensity	Before	6.33+1.08	(2-10)	0.002
	After	3.66+1.1	(0- 9)	

Drug doses were from 0.5 to 3 mg/kg/day, the most effective doses being between 1.5 and 2 mg/kg/day. Following lamotringine usage, the percentage of patients with severe, moderate, mild and no intensity, changed from 23.8 to 14.3%, 66.7 to 28.6%, 38.1% to 9.5 % and

19% to zero respectively. Man Whitney U and Chi square tests showed that there was no significant difference for sex or age between groups that showed improvement and those that did not.

Of the improved patients, 66.5% had reduction or complete improvement in just their aura. In 42.8% of patients, lamotringine was effective on both aura and headaches.

Discussion

In adult females, the prevalence of migraine headache is 5 fold that of adult males (1); however in children migraine occur equally in both genders,(3), findings similar to the results of our study.

The dose of lamotringine, most effective in the prophylaxis of migraine headache, ranged between 0.5 and 2 mg/kg/day. Unfortunately we were unable to find any similar studies on children to compare ours with. Studies on adult migraine with aura have used doses ranging between 75 to 150 mg/day for prophylaxis (4, 16).

This study showed that lamotringine was effective in reducing the frequency and intensity of migraine with aura. In this regard significant reduction was seen in the intensity of attacks following lamotrigine administration. Improvement of aura and headache was seen in 42.8% of cases and improvement of aura in 66.5%.

Studies on adult migraine with aura have also demonstrated a significant reduction in frequency and intensity of migraine with aura (4, 16, 17). The effectiveness of lamotrigine on the frequency of adult migraine with aura has been reported to be between 50 (4, 10, 13, 15) to 80% (17).

Lamotringine probably, suppresses glutamate release, which could be the main reason for the prophylactic effect of this drug on migraine with aura. Glutamate, as the key neurotransmitter is involved in the development and propagation of the neurophysiological correlate of the aura (8). Plasma and cerebrospinal glutamate levels have been shown to be higher in migraine with aura in comparison to migraine without aura (13). Therefore, if high glutamate levels should be responsible for cortical spreading depression and the clinical symptoms of migraine aura, lamotrigine might suppress this phenomenon and thus prevent aura development. The effective suppression of aura symptoms of lamotrigine may be due to the potent presynaptic and postsynaptic inhibition of glutamate, indicating that lamotrigine may act as an NMDA (N-methyl-D-aspartic acid) antagonist (18, 19).

In conclusion, lamotringine is effective in reducing migraine aura and intensity of attacks in migraine with aura and is an appropriate drug for the prophylactic therapy in children with classic migraine.

The results of this study showed that in children, migraine frequency was higher, duration was shorter and that visual and gastrointestinal problems were the most auras among them, results that are confirmed by other studies (3, 5).

Of the study limitations that deserve comment, first, there was no placebo control group to be compared. Of course, having a placebo group for 6 months or more was not ethical. Second, we did not measure the serum concentration of the drug. Perhaps, the serum concentration of lamotringine, compared to the administered dose would be a better guide to evaluate the clinical response, and we suggest this be considered in future studies

Acknowledgement

We would like to thank the parents of patients for their kind cooperation.

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