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Lamotrigine Effectiveness Against Classic and Common Migraine

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Abstract: Lamotrigine is effective in migraine with aura (classic migraine). However, its usefulness in migraine without aura (common migraine) is not clearly established. The purpose was to investigate the activity of lamotrigine on migraine with aura in comparison with any activity on migraine without aura in younger patients. In the study, 155 patients aged 4-14 years, suffering migraine headaches were diagnosed using International Headache Society (IHS) criteria. About 24 (15.5%) patients suffered classic migraine and 131 (84.5%) had common migraine. Each patient was prescribed lamotrigine (0.5 up to 3 mg/kg/day) for 6 months and evaluated monthly. Migraine frequency and intensity were recorded for 2 months before drug usage and 6 months during lamotrigine administration (acetaminophen was prescribed if needed). Lamotrigine induced a 45.2 and 17.1% reduction in the frequency of migraine attacks with and without aura, respectively. It also produced a 41.3 and 28.9% reduction in intensity of migraine with and without aura, respectively. About 14 patients in the classic migraine group and 23 patients in common migraine group were markedly improved ($p<0.001$). The results demonstrate that in younger patients, lamotrigine reduces both frequency and intensity of migraine in the presence and absence of aura.

Key words: Common migraine, classic migraine, headache, lamotrigine, aura, Iran

INTRODUCTION

Migraine headache is a neurological disorder associated with significant impairment of quality of life (Terwindt *et al*., 2000; Lipton *et al*., 2000). It affects about 17% of women, 6% of men and 4% of children annually (Silberstein *et al*., 2002). Among those patients who undergo treatment, less than one-third report consistent effectiveness with their current pharmacological regimens (Brandes, 2002). Furthermore, overuse of drugs for acute therapy of migraine headache can lead to chronic headache (Limmroth *et al*., 2002). Therefore, preventative medication in migraine headache is recommended, especially for patients in whom migraine attacks have a high frequency.

It has been hypothesized that migraine headache results from neuronal hyperexcitability (Welch *et al*., 1990). This has prompted research endeavor on antiepileptic medicines for migraine prophylaxis (Chronicle and Mulleners, 2004). Release of glutamate from platelets and neurons may constitute an important step in triggering neuronal depolarization and the occurrence of migraine auras. Therefore, drugs that interfere with the effect of glutamate on hyperexcitable neurons may prevent migraine attacks associated with aura (Cananzi *et al*., 1995). Lamotrigine is an antiepileptic drug which blocks voltage-dependent sensitive cation channels leading to inhibition of neuronal glutamate release (Lees and Leach, 1993). This liberation of glutamate is essential in the propagation of cortical spreading depression which is believed to be central to the genesis of migraine attacks, especially in migraine with aura (Lauritzen, 1994).

The value of lamotrigine in this type of migraine has been confirmed in some studies (Lampl *et al*., 1999; Chen *et al*., 2001; D'Andrea *et al*., 2002; Pascual *et al*., 2004). However, the usefulness of lamotrigine on migraine without aura, in which the cortical events triggered by glutamate are not present or weak is not clearly established. Some studies have claimed that lamotrigine is not effective on the frequency of migraine without aura (Vikelis and Rapoport, 2010). In this study, therefore the effect of lamotrigine was evaluated in migraine with aura (classic migraine) in comparison with any observable activity on migraine without aura (common migraine) in younger patients.

MATERIALS AND METHODS

The clinical trial was conducted at the neurology clinic of Shahrekord University of Medical Sciences, Iran. Diagnosis was made according to International Headache Society (IHS) criteria (Anonymous, 1988) and 155 patients within the age range 4-14 years were entered in the trial

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from them 24 (15.5%) patients suffered classic migraine and 131 (84.5%) had common migraine. After neurological examination and an EEG for each patient, a brain Computed Tomography (CT) scan was obtained if it was necessary. Patients who had other causes of headache were not able to tolerate lamotrigine had taken lamotrigine within 3 months prior to the trial had cardiac, hepatic or renal diseases or hypersensitivity to lamotrigine were excluded from the trial. An incidence of two migraine attacks per month was the minimum frequency criterion for study inclusion.

All patients received lamotrigine for 6 months and were evaluated monthly. The intensity of migraine headaches was recorded for 2 months before drug usage and during the 6 months of lamotrigine administration. Migraine intensity was scored as either pain free (none) or on an additional verbal/numerical 9-point headache scale analogous to the mild, moderate or severe 3-point scale of the International headache society clinical trials subcommittee (Tfelt-Hansen *et al*., 2000). Improvement criteria were considered as a 50% reduction in the frequency of migraine attacks and an intensity reduction to none or mild.

Parents of patients completed the questionnaire on behalf of patients who were not able to record the intensity and duration of mograine attacks. The starting dose of lamotrigine was 0.5 mg/kg/day and in those patients not responding to the initial drug dosage it was increased gradually (up to 3 mg/kg/day) until the frequency and intensity of attacks decreased to the above mentioned criteria levels. These doses were then continued up to the end of the trial.

Drug doses were not increased in patients who experienced undue drowsiness, dizziness or nausea. Throughout the trial period, acetaminophen was prescribed if it was necessary.

The intensity of migraine attacks was recorded prior acetaminophen ingestion. The study was approved by the ethical committee of Shahrakord University of Medical Sciences and written pediatric proxy informed consent was obtained by the parents of each patient eligible for the trial. Data were analyzed by SPSS 16 using one way ANOVA followed by Least Significant Difference (LSD) or student's t-test. $p<0.05$ was considered as significant.

RESULTS AND DISCUSSION

From the total 155 patients who entered the study, 3 patients with classic migraine and 15 patients with common migraine were not able to tolerate lamotrigine. The overall majority of patients (60.6%) who completed the study were female and out of the 137 patient total, 21 (15.3%) individuals suffered classic migraine and 116 (84.7%) patients had common migraine. In the classic migraine group, there were 8 males and 13 females and the common migraine group consisted of 46 males and 70 females ($p>0.05$). The average age of patients was 9.6±2.4 years and their mean duration of suffering with migraine was 2.8±1.4 years.

The most common auras in patients were visual in nature (43%) and there was no significant difference ($p>0.05$) between males and females in their intensity or frequency of pre-lamotrigine migraine attacks. Subsequently, lamotrigine induced a 45.2 and 17.1% significant reduction in the incidence frequency of migraine attacks with and without aura, respectively (Table 1). It also produced a marked 41.3 and 28.9% reduction of intensity scores in migraine with and without aura, respectively (Table 1). In the 137 patients who completed the trial, 37 individuals (27%) showed a marked improvement. Amongst the improved patients, 14 subjects (66.7%) belonged to the classic migraine group and 23 (19.8%) were in the common migraine group ($p<0.001$). In the classic migraine group, improvement was observed in 66.7% of patient auras and 42.8% occurred in auras and plus headaches.

The current study aim was to compare the effect of lamotrigine in young migraineurs with and without aura. The results showed that lamotrigine reduced both the frequency and intensity of migraine in the presence and absence of aura. A report from a previously conducted trial on lamotrigine in migraine has shown that it is statistically beneficial as a prophylactic agent for migraine with aura but this finding was not reproduced on migraine in the absence of aura (D'Andrea *et al*., 1999). The lack of effect described in migraine without aura may have been due to the low number of cases included (5 patients) in the before mentioned study. It was logical if we had employed a placebo control group to exclude any reduction in frequency and severity by natural variation

Table 1: The effect of lamotrigine on frequency and intensity of classic and common migraine in patients aged 4-14 years

		Frequency (per month)			Intensity score (0-10)		
Migraine	n	Before treatment	After treatment	Reduction (%)	Before treatment	After treatment	Reduction (%)
Classic migraine (with aura)	21	4.2±0.4	2.3±0.2	45.200	5.8±0.6	3.4±0.4	41.3
Common migraine (without aura)	116	4.2±0.2	3.5±0.1	17.100	5.9±0.2	4.2±0.2	28.9
Significance (p-value)	-	>0.05	<0.001	<0.001	>0.05	<0.05	<0.05

Values are mean±standard deviation

of the disorder, however we could not include this group due to ethical problems. Lamotrigine is an antiepileptic drug which blocks voltage-sensitive sodium channels, leading to inhibition of neuronal glutamate release. Glutamate is an important excitatory neurotransmitter in the central nervous system (Maragakis and Rothstein, 2001) and plays a major role in the pathophysiology of both epilepsy and migraine (Sherwin *et al*., 1988). Oral intake of glutamate induces migraine-like symptoms (Schaumburg *et al*., 1969) and an increased glutamate concentration has also been found in the plasma of migraine patients during their attacks (Ferrari *et al*., 1990). Moreover, higher concentrations of glutamate have also been demonstrated in the cerebrospinal fluid of migraine patients compared to controls (Martinez *et al*., 1993).

Glutamate appears to play an essential role in initiation, propagation and duration of spreading depression by acting on N-Methyl-D-Aspartate (NMDA) receptors, a phenomenon which is implicated in the pathophysiology of migraine attacks (Marrannes *et al*., 1988). Additionally, NMDA-mediated transmission seems to be involved in nociceptive transmission within the trigeminovascular complex, the neuronal system responsible for the transmission of pain in migraine (Goadsby and Classey, 2000). Hence, central sensitization of the trigeminal system may also be involved in the pathogenesis of migraine (Peres *et al*., 2004).

It has been shown that plasma glutamate levels are significantly increased in patients affected by both types of migraine in comparison with healthy matched controls. However, this increase is more marked in migraine patients with aura (95%) in contrast to those without aura (45%) when compared with controls (Vaccaro *et al*., 2007). Interestingly, glutamate concentrations have also been reported to be increased in the blood platelets of patients affected by migraine with aura (Cananzi *et al*., 1995).

A correlation can be seen between the results of the above studies and the effects of lamotrigine on migraine in the present trial. Hence, lamotrigine significantly reduced the intensity and frequency of both types of migraine (41.3 and 46% in migraine with aura, in addition to 28.9 and 17.1% in migraine without aura, respectively). The effect of lamotrigine on migraine with aura may be ascribed to a greater release of glutamate in this type of migraine. Thus, an abnormal release of glutamate in the intrasynaptic space causes an increased excitability of the cerebral cortex in addition to the development of spreading depression with which lamotrigine interferes. Migraine aura as a clinical manifestation of cortical spreading depression is caused by changes in ion homeostasis via glutamate (Lauritzen, 1994). Therefore, a marked reduction of migraine aura following lamotrigine may well be due to reduction of glutamate release. In support of this concept, blockade of NMDA receptors by ketamine in the rat causes inhibition of cortical spreading depression (Gorelova *et al*., 1987).

CONCLUSION

It might be said that the pharmacological effect of lamotrigine is closely correlated with levels of glutamate, the greatest clinically observed effect being expressed on migraine with aura.

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