

EFFICACY OF FLUNARIZINE IN THE PROPHYLACTIC TREATMENT OF MIGRAINE

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SUMMARY : *Flunarizine, a non selective calcium antagonist is being considered as an agent for the prophylactic treatment of migraine among its multiple physiologic effects, it prevents influx of calcium into vascular smooth muscle cells, protects brain against hypoxia, has antihistaminic activity and antiserotonin activity. In this study thirty-five patients with classical or common migraine were treated for three months with a single night dose of 10 mg flunarizine 13 of them (37.0 %) showed complete elimination of migraine symptomatology, 16 of them (45.7 %) a significant improvement, 3 of them (8.6 %) slight improvement, 3 of them (8.6 %) no effect at all. Below the age of 35, complete recovery was significantly high ($p < 0.01$). There was no difference in the efficacy of the drug between the two migraine types.*

Key Words : *Migraine, Flunarizine, Prophylactic Treatment.*

INTRODUCTION

Despite questions that remain regarding the pathogenesis of migraine various drug therapies have been found empirically to be effective for the symptomatic and prophylactic treatment. Yet there is a clear need to continue the exploration of potentially useful drugs in the prevention of migraine attacks.

According to prevailing vascular theory based on pioneering work of Wolff and Graham, a migraine attack begins with vasoconstriction that produces prodrome and is followed by vasodilatation that results in the typical throbbing headache (2, 12, 13). Recent experimental data have also suggested roles of brain hypoxia and serotonin in the chain of events leading to migraine symptoms.

Studies by Olesen, Lauritzen, Lance and Mos-

kowitz have promoted the neurogenic theory which states that there is a consistent decrease in neuronal activation and rCBF which begins in the occipital region during the aura phase and slowly spreads forward in the ipsilateral hemisphere at a rate of about 3 mm/min (10). The available evidence now suggests that migraine may be due to an intermittently occurring paroxysmal neuronal discharge from serotonergic neurons in the median raphe nucleus of pons. These nuclei project strongly to the ipsilateral occipital cortex where the initial discharge is believed to initiate a wave of spreading excitation, followed by the aforementioned depression of neuronal activity (9).

Since 1981 numerous studies have shown that a new class of pharmacological agents, the calcium channel blockers are effective in the prophylaxis of migraine. These drugs inhibit the entrance of extra-

cellular calcium into cephalic vascular smooth muscle cell and thus block the intracerebral vasoconstriction induced by vasoactive neurotransmitters such as serotonin and norepinephrine. The ability of calcium channel blockers to block the postsynaptic serotonin receptor subtype (5HT₂) on the cerebral blood vessels and brain neurons is considered an essential contributing factor to the efficacy in migraine. These drugs are thought to prevent migraine also by inhibiting platelet serotonin release and uptake (3, 4, 8, 11). Among the calcium channel blockers flunarizine is a nonselective calcium antagonist which is highly lipophilic and passes blood-brain barrier and reaches the brain in significant quantities. Numerous controlled studies have established its efficacy in prophylaxis of migraine. Besides its effect in prophylaxis of migraine in adults and children, flunarizine has also been successfully employed to treat migraine attacks.

The present study was undertaken in a group of migraine patients with and without aura in order to investigate the efficacy of flunarizine in migraine prophylaxis.

MATERIALS AND METHODS

Thirty-five patients seen in the neurology outpatient Clinic of Akdeniz University Hospital with a diagnosis of migraine were eligible for admission to the study. The selection was based on two basic criteria.

1) A diagnosis of either classic or common migraine according to the criteria of headache classification committee of the International Headache Society.

2) A frequency of severe, long duration migraine attacks of at least once per week based on the average of the last three months before admission.

Before entering the study, patients underwent a complete physical and neurological examination and those who had diseases contraindicating treatment with calcium blockers were excluded.

27 (77.1 %) patients were diagnosed as common and 8 (22.9 %) patients as classic migraine, of whom 30 (85.7 %) were women and 5 (14.3 %) were men. Their ages ranged between 16 and 48 years (average 34.1 years). Patients' history of migraine ranged from 6 months to 30 years, the usual duration of attacks ranged between 1 and 24 hours.

The study consisted of an initial 12 week flunarizine treatment period. Each patient was instructed to take 10 mg flunarizine every evening. Patients were seen in the clinic at 4 week intervals and they were required to complete a diary including the frequency, duration and severity of the attacks. The appearance of any side effects were also recorded. In the nominal analysis, Fisher's exact and chi-square tests were used.

RESULTS

35 patients completed the trial for three months. 13 of these patients refused to discontinue the drug and took for more than three months.

The efficacy of flunarizine as divided into four groups is shown in Table 1 and Figure 1. First group as (+++) is the group who showed complete elimination of migraine symptomatology, second group as (++) showed significant improvement in frequency, severity and duration of attacks, third group as (+) showed slight improvement and fourth group (-) showed no effect at all. The overall appreciation was very convincing. Flunarizine treatment reduced the frequency, severity and duration of the migraine attacks. Of the 35 patients, 13 (37.1 %) showed the complete elimination of migraine symptoms.

EFFICACY*	NUMBER OF PATIENTS					
	Males	%	Females	%	Total	%
+++	1	7.7	12	92.3	13	37.1
++	3	18.8	13	81.2	16	45.7
+	1	33.3	2	66.7	3	8.6
-	0	0.0	3	35	3	8.6
TOTAL	5	14.3	30	85.7	35	100.0

* EFFICACY
 +++ : Complete elimination of migraine symptomatology
 ++ : A significant improvement in frequency, severity and duration of attacks
 + : Slight improvement
 - : Effect at all

Table 1 : Efficacy of treatment with flunarizine.

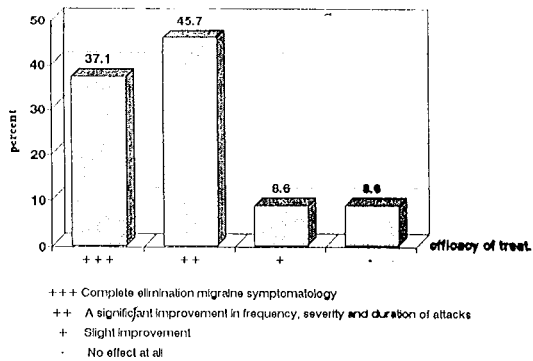


Fig - 1 : Frequencies of efficacy of treatment with flunarizine.

matology, 16 (45.7 %) a significant improvement, 3 (8.6 %) slight improvement and 3 (8.6) no effect at all.

In the follow up of the patients, there was an important reduction in the frequency, severity and duration of attacks already at the end of first month. Yet the percentage of complete recovery increased when the duration of the treatment period exceeded three months. Below the age of thirty-five, complete recovery was significantly high ($p < 0.01$). There was no difference of efficacy of flunarizine between the two migraine type groups ($p > 0.05$).

Side-effects : The side effects observed during the therapy were seen in 11 patients which were sedation (3 patients), insomnia (3 patients), fatigue (2 patients), weight gain (2 patients), ataxia (2 patients) and skin rash (2 patients). One patient had two and another patient had three side effects at the same time.

DISCUSSION

The multiple studies reviewed all support the conclusion that calcium channel blocking drugs are effective in the prophylaxis of migraine. Double-blinded and comparative studies with nimodipine, verapamil, nifedipine, diltiazem and flunarizine all showed these drugs to be significantly better than placebo. It has been suggested that the mechanism of action of flunarizine is with its anti-hypoxic / ischemic properties. Moreover this drug has been shown to be able to antagonize the vasoconstriction induced by several agents including serotonin and norepinephrine and has been shown to antagonize

the actions of histamine by blocking H1 histamine receptors and prostaglandins. Flunarizine besides all these properties also reduces spreading cortical depression (1, 7, 9, 14).

Louis in his double blind study compared flunarizine with placebo and found a significant reduction in frequency but not in severity and duration of attacks. In this study younger patients appeared to respond better to treatment and during the third month, 83 % of the treated patients were completely attack-free (7).

Diamond also in his single blind crossover study found a statistically significant reduction in headache incidence and/or severity with flunarizine treatments for 2-6 months (4).

D'Amato et al, evaluated the efficacy of long term (one year) migraine prophylaxis with flunarizine and found a reduction of frequency to about half of the pre-treatment level in one to three months time. The condition remained more or less stable from the third month onwards (3).

There are also other double-blind trials published concerning the efficacy of flunarizine in adult migraine patients which all show its significantly prophylactic effect in reducing the frequency and/or severity and duration of the attacks (6).

Our results have showed also the significant efficacy of flunarizine in the prophylactic treatment of migraine patients with or without aura. Moreover younger patients have responded better to treatment and duration of the treatment and duration effected the efficacy.

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