International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 2 Issue 4, April 2015

ISSN: 2394-4404

Safety And Efficacy Of Flunarizine In Childhood Migraine: A Retrospective Study Of 10 Years

Rajesh Kumar

Associate Professor, Department of ENT,
Institute of Medical Sciences,
Banaras Hindu University, Varanasi, India

Sangita

Second Year, Department of E.N.T,
Institute of Medical sciences,
Banaras Hindu University, Varanasi

Amit Gupta

Ex Resident, Department of E.N.T,
Institute of Medical sciences,
Banaras Hindu University, Varanasi

Abstract: ***Headache ranks ninth among the causes of visit to physicians. Headache can results from distortion, stretching, inflammation, or destruction of pain sensitive nerve endings as a result of intra or extra cranial diseases. The overwhelming majority of headaches are either migraine or so called tension headaches, with both abnormalities frequently playing a role in given individual. The prevalence of migraine rapidly increase in first and second decades of life, remains at the same level until the fourth or fifth decade, then decline slowly but steadily with the advancement in the age. We present here a 10 years retrospective study of the use of flunarizine in childhood migraine with focus on safety and efficacy. In our cohort of children with migraine, flunarizine appears to be more effective in the hemiplegic migraine group. Adverse effects were seen in one fifth of the individuals, leading to discontinuation in 18%.***

Keywords: Childhood migraine, flunarizine, Hemiplegic migraine.

I. INTRODUCTION

Migraine is one of the most common painful conditions of the mankind. This is known to us through writing science as early as 3000 B.C. Migraine is found in 5 to 10% of the population and in as much higher proportion (15%) of women during their reproductive years. Migraine is a French word derived from megrim which in turn was derived from the Latin hemicrania and its corrupted forms hemigranea and migranea.

Migraine is common neurological problem in children that can cause considerable disability. The symptomatology can vary considerably that from adults, which is reflected in the International Headache Society's revised diagnostic criteria (2004).

Management of migraine is multimodal, including pharmacological and non-pharmacological strategies. Factors which influence the need for preventive therapy include attack severity, frequency and impairment of social and educational activities. A wide range of pharmacological agents such as anti hypertensives, antiseratoninergics, antidepressants, anticonvulsants, and calcium channel blockers have been used for this purpose with variable rate of success. Hemiplegic migraine, in which the aura symptoms include motor weakness, poses a particular challenge as the diagnosis is often delayed and no specific preventive agent has been found to be effective.

Flunarizine, a long acting calcium channel blocker, was originally introduced in the 1970's for the treatment of occlusive vascular diseases. The mechanism of action of flunarizine in migraine is unclear, although its calcium and dopaminergic antagonism may offer some insights into possible subcortical brain targets. Several studies have demonstrated its efficacy in migraine prophylaxis in adults.

II. MATERIAL AND METHODS

We collected the patients for the above study from ENT and Pediatrics departments. Individual with the diagnosis of

migraine and who had at least one follow up assessment and a minimum of 3 months treatment with flunarizine were included in the study. Headache diagnosis was based on International Classification of Headache disorders.

ICHD2 code	Category	Number of individuals
1.1	Migraine without aura	**44**
1.2.1	Typical aura with migraine headache	**13**
1.2.5	Sporadic hemiplegic migraine	**8**
1.2.4	Familial hemiplegic migraine	**5**
1.3.2	Abdominal migraine	**1**
1.3.3	Benign paroxysmal vertigo of childhood	**1**

Table 1: Diagnosis: subcategories

A total of 130 children were initially identified. Of these, 100 children (59 males; 41 female; mean age 13 years; age range 3years 6months - 17 years; listed in table 1) were included in the final analysis(Fig.1). Thirty children were excluded for the following reasons: 13 had not had a follow-up assessment at the time of study, 9 were non migraineurs, 4 had incomplete medical records, and 4 had an inadequate treatment duration (< 3 months).

Foe each individual, following data were collected: basic demographic details, diseases characteristic before and after treatment with flunarizine, prophylactic medications tried before flunarizine, dose and duration of treatment with flunarizine, side effects, and reasons for the discontinuation of flunarizine.

Therapeutic outcome was measured by analyzing the frequency of attacks before and after starting treatment. Successful prophylaxis was defined as a 50% reduction in frequency of attacks over a period of 3 months. In most cases, frequency of attacks was based on the recollection of individual care giver.

Preventive medication	Number of individuals
Pizotifen	48
Propranolol	35
Amitriptyline	23
Topiramate	15
Sodium valproate	9
Gabapantine	8
Carbamazepine	4
Clonidine	2

Table 2: Preventive medicine used

III. RESULTS

STATISTICAL ANALYSIS - Summary data are presented as median and ranges.

The median duration of the disease until referral was 4 years (range 5 months-13 year). The duration was shorter in individuals with hemiplegic migraine (3y 1mo) than in individuals with non hemiplegic migraine (4years). Apart from six, all individuals had tried at least one preventive medication before trying flunarizine therapy. An average of three preventives (range 1-10) had been tried per individual before commencement of flunarizine. Table 2 lists these medications and the number of children that used each of these medications.

MIGRAINE CHARACTERISTICS

The median duration of migraine of migraine at the time of commencing flunarizine therapy was 4 years and 10 months (range 6mo-14 years). The median frequency of attacks for the entire cohort was 7 per month (range 0.5-30 months). The frequency of attacks was four per month (range 0.3-12) in the group with hemiplegia and 13 per month in the remainder.

FLUNARIZINE DOSING

The initial dose of flunarizine for the individuals was determined. The standard dose was 5 mg. Dose escalation was made when there was no response to the starting dose or in order to optimize response to treatment. This was done at the first follow up.

Flunarizine treatment was commenced after a median interval of 6 months (range 2mo-4 years) after referral to the hospital. The interval was similar in the group with or without hemiplegic migraine (6 months). The starting dose of flunarizine was 5 mg in 62 individuals, 10 mg in six, 2.5 mg in three, and 7.5 mg in one. The dose was escalated in 43 individuals after a median duration of 5 months (range 3months to 8 years).

DURATION OF USE AND TOLERABILITY

Individuals were followed up for a median of 24 months (range 3months-9 years), at 6 months intervals, with follow up on telephone, if needed. The duration of use of flunarizine in this cohort was 12 months (Range 3 months - 8 years).

SIDE EFFECTS

Of 89 individuals who started treatment with flunarizine, side effect data were available in 76, including all 100 individuals in the final cohort. Of 100 patients 21 experienced the side effects: depression or mood swings in seven, weight gain and / or increased appetite in six, tiredness or sedation in three, worsening in headache in three, and both tiredness and worsening of headache in two. Eighteen individual discontinued the treatment, whereas the remaining three continued despite feeling tired as their migraine frequency had improved. Of the six individuals who were not included in the cohort owing to inadequate treatment duration, three developed tiredness leading to withdrawal within 6 weeks. The incidence of side effects in this cohort of 100 individuals was 29%. All side effects resolved promptly on cessation of therapy.

IV. DISCONTINUATION

Flunarizine was discontinued in 44 individuals: 22 individuals discontinued after a median interval of 7.5 months (range 3-23 months) because of lack of response, and 16

because of side effects, and in 6 children the drug was withdrawn after a median duration of sixteen months following complete remission of migraine.

THERAPEUTIC OUTCOME

Fifty seven individuals experienced at least 50% reduction in frequency in attacks (table 3). A reduction in frequency of less than 50% was seen in seven individuals, while no change was seen in thirty five individuals. An increase in attack was observed in one individual.

Type	Improved	Slight improvement	No improvement	Worsening
All form of migraine	57%	7%	35%	1%
Hemiplegic migraine	85%	7%	1%	0
Other subtype	51%	7%	41%	1%

Table 3: Headache outcome (%)

V. DISCUSSION

This is a retrospective study in a highly selected individual group, thus limiting the conclusion that can be drawn from the data. A systematic Cochrane review of migraine prophylactics in children found beneficial effect for only two drugs, namely propranolol and flunarizine, from a small pool of data, that is one study for each drug. There is now emerging evidence that topiramate is also effective Few studies have been carried out to date regarding the effectiveness and side effects of flunarizine in children with migraine. A double blind, placebo controlled crossover trial of 70 children conducted by Sorge et al. in late 1980s showed a significant reduction in frequency and duration of attacks. The reported side effect in this study were weight gain in 22% and drowsiness in 9%. A similar side effect profile has been noted in other adult studies. A large study in adults comparing treatment with flunarizine and propranolol found that the incidence and severity of the side effects were similar in the two groups.

In this study side effect were reported in 21% of the children, leading to discontinuation of the treatment in the majority of the affected children. Depression and/ or mood swings were the commonly seen side effects. In one children there was a past history of depression which appeared to have been reactivated by flunarizine. Actual weight gain was only seen in one child, with the remainder of cases reporting perceived weight gain or increased appetite. All the side effects resolved on the discontinuation of treatment. The side effect profile in this cohort was more or less similar to that seen in previous adult and pediatric studies.

In term of efficacy, 57 children in this cohort benefited by way of reduction in attack frequency. This is comparable to the outcome data already available from the adult and pediatric studies. However, of note is the relatively higher rate of therapeutic efficacy in hemiplegic migraine (85% vs51%) in this cohort.

In term of treatment duration, 3 months are considered adequate to assess efficacy in adults. In children longer duration has usually been necessary to reach therapeutic efficacy, as seen in our cohort. Our experience has led us to regard flunarizine as treatment of choice for hemiplegic migraine.

VI. CONCLUSION

Within the limitation associated with the highly selective nature of the individuals, flunarizine appears to be effective in reducing the attack frequency in childhood migraine in 57% of children in this cohort, which is consistent with the published data. The efficacy, however, appears to be much higher (85%) in children in hemiplegic migraine than in those with other type of subtypes. We use flunarizine as first line medication in children with hemiplegic migraine. Reversible side effect were seen in about one in five of the children studied, with depression and weight gain or increased appetite being the commonest. A multicentre prospective, blinded randomized controlled trial would be needed to substantiate the therapeutic difference observed between children with and without hemiplegic or non hemiplegic migraine.

REFERENCES

[1] Tkachuk GA, Cottrell CK, Gibson JS, O'Donnell FJ, HolroydKA. Factors associated with migraine-related quality oflife and disability in adolescents: a preliminary investigation.Headache 2003; 43: 950–5.
[2] Lateef TM, Merikangas KR, He J, et al. Headache in anational sample of American children: prevalence and comorbidity.J Child Neurol 2009; 24: 536–43.
[3] Lipton RB. Diagnosis and epidemiology of pediatricmigraine.CurrOpinNeurol 1997; 10: 231–6.
[4] Headache Classification Subcommittee of the InternationalHeadache Society. The International Classification of HeadacheDisorders: 2nd edition. Cephalalgia 2004; 24 (Suppl. 1):9–160.
[5] Evers S, Afra J, Frese A, et al. EFNS guideline on the drugtreatment of migraine–revised report of an EFNS task force.Eur J Neurol 2009; 16: 968–81.
[6] Russell MB, Ducros A. Sporadic and familial hemiplegicmigraine: pathophysiological mechanisms, clinical characteristics,diagnosis, and management. Lancet Neurol 2011; 10:457–70.
[7] Goadsby PJ, Charbit AR, Andreou AP, Akerman S, HollandPR. Neurobiology of migraine. Neuroscience 2009; 161:327–41.
[8] Diener HC, Matias-Guiu J, Hartung E, et al. Efficacy andtolerability in migraine prophylaxis of flunarizine in reduceddoses: a comparison with propranolol 160 mg daily. Cephalalgia2002; 22: 488.
[9] Victor S, Ryan SW. Drugs for preventing migraine headachesin children. Cochrane Database Syst Rev 2003; (4):CD002761.
[10] Lewis D, Winner P, Saper J, et al. Randomized, doubleblind,placebo-controlled study to evaluate the

efficacy andsafety of topiramate for migraine prevention in pediatricsubjects 12 to 17 years of age. Pediatrics 2009; 123: 924–34.

[11] Sorge F, De Simone R, Marano E, Nolano M, Orefice G,Carrieri P. Flunarizine in prophylaxis of childhood migraine.A double-blind, placebo-controlled, crossover study. Cephalalgia1988; 8: 1–6.

[12] Lu¨cking CH, OestreichW, Schmidt R, Soyka D. Flunarizinevs. propranolol in the prophylaxis of migraine: two doubleblindcomparative studies in more than 400 patients. Cephalalgia1988; 8 (Suppl. 8): 21–6.

[13] Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS.Comparison of the efficacy and safety of flunarizine to propranololin the prophylaxis of migraine. Can J NeurolSci1992; 19: 340–5.

[14] Visudtibhan A, Lusawat A, Chiemchanya S, Visudhiphan P.Flunarizine for prophylactic treatment of childhoodmigraine. J Med Assoc Thai 2004; 87: 1466–70.