

Flunarizine for Prophylactic Treatment of Childhood Migraine

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Objective : To determine the effectiveness of flunarizine for migraine prophylaxis in children.

Patients and Method : Children aged between 7 and 15 years who had the indication for prophylactic treatment of migraine were recruited into a prospective study at the Department of Pediatrics, Ramathibodi Hospital, from January 1st to December 31st 1999. After verbal consent was obtained, flunarizine was administered either at 5-mg daily in those who had never received it or at 10-mg daily in those who previously took this drug within one year. Serial evaluation for the severity of migraine including duration, intensity, and frequency of headache attacks was performed every 2 weeks for 6 months.

Results : Twenty-one children (10 boys, 11 girls) with a mean age of 11.3 ± 2.48 years (range 7-15 years) were enrolled in the study. There were ten children who had migraine with aura. Initially, 5-mg daily and 10-mg daily of flunarizine were administered in 19 and 2 patients respectively. The dosage was increased to 10-mg daily after two weeks in 5 patients because of the unresponsiveness to the initial dose. Improvement was observed in 14 patients (66%) including 13 of 14 patients who received 5-mg daily and 1 of 7 patients who received 10 mg daily. Five patients (23%) had no recurrent attack. Nine patients (42%) had more than 50% reduction of frequency of migraine and 3 of these had either shorter duration or less intensity of the attack. Clinical improvement was observed between 2 and 4 weeks after initiation of treatment. There was no adverse effect observed.

Conclusion : This is a preliminary result demonstrating that flunarizine is one of the effective drugs for migraine prophylaxis in children.

Keywords : Flunarizine, Migraine, Headache, Children

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Migraine is one of the common problems in children. Estimated prevalence in preschool aged and school aged children ranged from 3.2% to 10.6%⁽¹⁻⁴⁾. Though the severity of this illness is not as great in children as it is in the adults, it may disturb normal life of the affected children and their parents. Occasionally, complicated variants, including hemiplegic migraine which is identified as an autosomal dominant condition and basilar migraine, may occur and can lead to focal neurological deficits⁽⁵⁾.

For those with frequent migraine attacks, prevention of further migraine may be indicated⁽⁶⁾.

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There are drugs for prophylaxis of migraine such as beta-blockers, antidepressants, nonsteroidal anti-inflammatory drugs and anticonvulsants^(7,8). Calcium channel blocker has been proved to be an effective prophylactic drug in adult patients⁽⁹⁾. Despite the efficacy in children demonstrated by Sorge et al in 1988, the recommended dosage in children has not been well established and there were few studies in children reported thereafter^(10,11). The authors, therefore, would like to reevaluate the efficacy and the adverse effects of this medication in the prevention of migraine in Thai children.

Material and Method

From July 1st to September 30th 1999, children aged between 7 and 15 years with headache who

presented at the Division of Neurology, Department of Pediatrics, Ramathibodi Hospital, were assessed. Diagnosis of migraine was made according to the International Headache Society's classification⁽¹²⁾. Those with fulfilled criteria for prophylactic treatment of recurrent migraine (Table 1) were recruited into the present study. After obtaining consent, the basic background information of each child including family history, socioeconomic status, school performance records, family relationship, parents' attitude to this illness were collected by interview and questionnaire. Physical and neurological evaluations were performed. If there were any focal neurological deficits, the child would be excluded from the study. Flunarizine (Sibelium) was then initiated at 5-mg daily for those who, had never received this drug. For those who had previously taken flunarizine within the past one year, 10-mg daily of flunarizine were initiated. Follow up evaluation every two weeks for one month and every month for a total duration of 6 months was performed. Severity of headache, which included frequency, duration and intensity of migraine headache, was evaluated by the headache calendar. At each follow-up evaluation, complete physical and neurological examination was performed.

Results

Twenty-one children comprised of 10 boys and 11 girls were enrolled in the present study. Their ages ranged from 7 to 15 years with an average age of 11.3 ± 2.48 years. Ten children were classified into classic migraine. Ten children had daily migraine attacks prior to the initiation of prophylactic treatment. Nine children had either a computerized tomographic scan (CT scan) or a magnetic resonance imaging (MRI) of the brain. There was one child who had a small lipoma at the meninges demonstrated by the CT scan which was not the explainable cause of headache. The rest of the brain imagings were unremarkable. The characteristics of headache in the studied children are demonstrated in Table 2.

Nineteen children were initially administered with flunarizine at 5-mg daily. Flunarizine at 10-mg daily was prescribed to the other two children who had previous treatment with flunarizine at 5-mg daily in the past 6 months without improvement. Among those who were initially given 5-mg daily, flunarizine was increased to 10-mg daily one month later because of the lack of improvement in five patients. There were 14 children in whom improvement of headache characterized as a decrease in frequency of migraine was

obtained. Shortened duration and reduction in the intensity of headache were obtained in 3 patients. The outcomes of treatment are shown in Table 3.

Table 1. Criteria for migraine prophylaxis

Prophylactic treatment of migraine	
1. Demonstrable disability	
- Absence from school > 2 days in one month	
- Interrupted daily activities > 2 days in one month	
2. Failure of abortive treatment	
3. Demonstrable contraindication in taking drug for abortive treatment	
4. Prolonged aura	
5. Demonstrable cerebral infarction	
6. Duration lasts > 3 days in one attack	
7. Attack > 2 times / week despite acute treatment	

Table 2. Characteristics of headache in enrolled children

	Number of patients	Percent
Characteristics (n = 21)		
Aura	10	47.6
Throbbing type	18	85.7
Unilateral headache	9	42.8
Bilateral headache	8	38.2
Alternating headache	2	9.5
Associated symptoms (n = 17)		
Nausea or vomiting	15	88
Phonophobia	0	0
Photophobia	2	12
Location of headache (n = 21)		
Temporal region	15	71.4
Forehead	2	9.5
Other area	4	19.1
Duration of headache (n = 21)		
< 2 hours	10	47.6
> 2 hours	11	52.4
Frequency of headache (n = 21)		
Daily	10	47.6
3-4 days/week	5	23.8
1-2 days/week	5	23.8
2-3 days/month	1	4.8

Table 3. Outcomes of prophylactic treatment with flunarizine

	Number of patients	Percent
Improvement	14	66.7
A. Decreased frequency of migraine	14	66.7
B. Shorter duration of headache	3	14.3
C. Decreased intensity of headache	3	14.3
No improvement	7	33.3
Total	21	100.0

Discussion

Migraine is one of the common neurological problems in children^(2,4,13,14). Prophylactic medication is recommended in those who experienced complicated migraine or have frequent recurrences^(6,9,11). Beta-blockers such as propranolol have proved to be useful in prophylactic treatment for years⁽¹⁵⁾. However, it might result in hypotension and it is also contraindicated in migraineurs who have hyperreactive airway diseases^(6,15). Serotonin antagonists such as pizotifen and cyproheptadine were not as effective as beta-blockers and might cause drowsiness as well as weight gain^(9,11,16). Anticonvulsants such as valproate, gabapentin and topiramate were reported to be effective in preventing migraine recurrence^(11,17-21). Serious adverse effects of these drugs such as hepatotoxicity and pancreatitis made them less attractive in prophylactic treatment of this illness in children^(22,23). Chronic treatment with non-steroid anti-inflammatory drugs such as naproxen and ibuprofen may result in gastritis, gastrointestinal discomfort and platelet dysfunction^(11,24). These drugs may increase the risk of bleeding in a certain viral infection such as dengue hemorrhagic fever, which is common in children in tropical countries such as Thailand. Flunarizine, a calcium channel blocker, has been used in the prophylaxis of migraine in adults for years^(15,25,26). There were studies demonstrating that this drug was as effective as high dose of propranolol in the prevention of recurrent migraine⁽²⁷⁻³⁰⁾. A randomized, double-open, clinical trial demonstrated that there was no significant difference between flunarizine and valproate in migraine prophylaxis⁽¹⁹⁾. Despite its attractive efficacy, there were not many studies in children^(9,10,31).

According to the study, flunarizine was able to prevent migraine recurrence. Sixty-six per cent of the presented patients demonstrated significant improvement of their symptoms, which was similar to the result observed in the adult patients^(15,25). Frequency of headache was the prominent improvement obtained from this drug. However, the improvement of the severity of headache, including decreased headache intensity and shortened duration of headache, was obtained in 14 per cent of the studied patients. This finding was in-line with the result obtained in previous reports in adult patients^(15,25). Though, the intensity and the duration of attack were not decreased by the therapy; the majority of the children and their parents reported overall improvement of daily activities because of the less frequency of the migraine attacks.

Concerning the initial dose of flunarizine, the dosage given in each patient in the present study was

similar to the dosage deployed in the double-blinded, placebo-controlled, cross-over study conducted by Sorge et al in 1988⁽¹⁰⁾. Efficacy obtained from a lower dose of flunarizine at 3-mg daily was not significant different from that of 10-mg daily⁽²⁸⁾. However, it is not practical in Thailand owing to the unavailable preparation of 3-mg tablets of flunarizine. Among 14 children who reported improvement of headache, there was only one child whose daily dosage of flunarizine was raised to 10 mg. This child's body weight was 61 kilograms; therefore a higher dose may be needed in some children whose weight is over 60 kilograms. There were seven children who either started taking 10-mg daily initially or subsequently did not have any benefit from higher dose. The authors proposed that 5-mg daily of flunarizine was the suitable initial dose in children older than 7 years.

The main mechanism of flunarizine in prevention of recurrent migraine is most likely to be the neurogenic effect in influencing the release of neurotransmitter such as dopamine and met-enkephalin and by blocking calcium and sodium channels^(25,32-34). It is less likely to be the vascular effect according to the failure of transcranial doppler sonography to demonstrate significant change in blood flow velocity measured in the middle cerebral artery and basal artery after treatment with intravenous flunarizine during a migraine attack⁽³⁰⁾.

Adverse effects of flunarizine which were the concerning issue in prophylactic treatment of migraine included drowsiness, dizziness, orthostatic hypotension, tingling sensation, and abdominal discomforts⁽⁸⁾. The presented patients neither reported nor had any of the adverse symptoms. The authors speculated that the initiation of low-dose and the short duration of treatment might be the explanation of this finding. At present there has been no definite recommendation regarding the duration of prophylactic treatment of migraine, a precaution should be exercised especially if longer duration of treatment is planned for any child.

Owing to the limitation of the present study which was conducted in a small group of children with an intention-to-treat basis during a short period of treatment; the present study was a preliminary result for physicians in considering flunarizine as an alternative drug for prophylactic treatment of migraine in children above 7 years of age. A randomized, double-blind, controlled study in a large group of patients with long duration of treatment should be conducted to provide definite conclusion in the future.

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การใช้ฟลูนาวิซีนในการป้องกันการเกิดอาการปวดศีรษะไมเกรนซ้ำผู้ป่วยเด็ก

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คณะผู้รายงานได้ศึกษาผลของฟลูนาวิซีนในการป้องกันการเกิดอาการปวดศีรษะไมเกรนในผู้ป่วยเด็กอายุระหว่าง 7 ถึง 15 ปีจำนวน 21 คนที่ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดีระหว่างเดือนมกราคมถึงเดือนธันวาคม พ.ศ. 2542 ผู้ป่วยทุกคนที่มีอาการปวดศีรษะที่มีลักษณะอาการครบตามแนวทางการวินิจฉัยอาการปวดศีรษะไมเกรนและมีข้อบ่งชี้ที่จะจำเป็นต้องได้รับยาป้องกันการเกิดอาการซ้ำ จะได้รับยาฟลูนาวิซีนในขนาด 5 มิลลิกรัมต่อวันในผู้ป่วยที่ไม่เคยได้รับยานี้มาก่อนซึ่งมีจำนวน 19 คน และในขนาด 10 มิลลิกรัมต่อวันในผู้ป่วยที่เคยได้รับยานี้ไม่เกิน 5 มิลลิกรัมต่อวันมาก่อนในเวลาหนึ่งปีที่ผ่านมาจำนวน 2 คน ผู้ป่วยทุกคนได้รับการติดตามอาการด้วยการใช้แบบสอบถาม การสัมภาษณ์ และการตรวจร่างกายเป็นระยะ ๆ ทุกหนึ่งเดือนเป็นเวลา 6 เดือน โดยประเมินความรุนแรง และความถี่ของการเกิดอาการปวดศีรษะ ตลอดจนผลอันไม่พึงประสงค์จากยา ผู้ป่วย 5 คนในกลุ่มที่ได้รับขนาดยาเริ่มต้น 5 มิลลิกรัมต่อวันได้รับการเพิ่มขนาดยาเป็น 10 มิลลิกรัมต่อวัน เนื่องจากไม่แสดงอาการตอบสนองต่อการรักษา ดังนั้นจึงมีผู้ป่วยจำนวน 7 คนที่ได้รับยาในขนาด 10 มิลลิกรัมต่อวันและจำนวน 14 คนที่ได้รับยาในขนาด 5 มิลลิกรัมต่อวัน พบว่ามีผู้ป่วยจำนวน 5 คนคิดเป็นร้อยละ 23 ที่ไม่เกิดอาการปวดศีรษะไมเกรนซ้ำ ผู้ป่วยจำนวน 9 คนหรือร้อยละ 42 ที่มีความถี่ของการเกิดอาการปวดศีรษะลดลงมากกว่าหรือเท่ากับร้อยละ 50 เมื่อเปรียบเทียบกับความถี่ที่เกิดอาการก่อนได้รับยานี้ ผู้ป่วยจำนวน 14 คนหรือร้อยละ 66 ที่ความรุนแรงโดยรวมของอาการปวดศีรษะไมเกรนลดลง ไม่มีผู้ป่วยที่มีอาการไม่พึงประสงค์จากยา คณะผู้รายงานมีความเห็นว่า ฟลูนาวิซีนสามารถใช้ป้องกันการเกิดอาการปวดศีรษะไมเกรนซ้ำในเด็กที่มีอายุมากกว่า 7 ปีได้โดยใช้ในขนาดเริ่มต้น 5 มิลลิกรัมต่อวัน การศึกษานี้เป็นการศึกษาเบื้องต้นซึ่งควรจะมีการศึกษาในผู้ป่วยจำนวนมากในระยะยาวต่อไป