EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

Management of migraine without aura in adolescents: The experience of flunarizine use in a Turkish cohort

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Background and purpose – Flunarizine is a specific calcium antagonist and is frequently used in adults for the prophylactic treatment of migraine. The use of flunarizine may lead to somnolence and weight gain, depression, and rarely extrapyramidal symptoms in adults. However, studies detecting the efficacy and safety of flunarizine use in adolescents are limited. In the current study, the effectiveness of flunarizine for the management of migraine without aura in Turkish adolescents was evaluated.
Methods – Forty-six patients with migraine without aura, receiving flunarizine 5mg per day were included. In this retrospective study, the medical records of the cases were examined. Visual Analog Scale (VAS) and MIDAS scores were compared to assess the efficacy of the 3 months treatment.
Results – The mean age was 14.37±1.83 years. There was a significant improvement in the VAS and MIDAS scores of the patients at the end of the third month ($p<0.05$). Side effects were detected in 23.9% of the patients, and these symptoms were sedation in 8.7% of the patients, mood swings in 4.3%, and vomiting in 4.3% of them. None of the patients discontinued the treatment due to side effects.
Conclusion – Although the advancement of migraine research and treatment is inevitable, our findings support that flunarizine should still be considered as an effective and tolerable treatment option in adolescent migraineurs.

Keywords: migraine, flunarizine, MIDAS

Az aura nélküli migrén kezelése serdülőknél: a flunarizinhasználat tapasztalatai egy török kohorszban

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Bevezetés – A flunarizin egy specifikus kalciumantagonista, amit felnőtteknél gyakran alkalmaznak a migrén profilaktikus kezelésére. A flunarizin alkalmazása felnőtteknél álmossághoz és testtömeg-gyarapodáshoz, depresszióhoz és ritkán extrapiramidális tünetekhez vezethet. A flunarizin serdülőknél történő alkalmazásának hatékonyságát és biztonságosságát kimutató vizsgálatok azonban korlátozottak. A jelen vizsgálatban a flunarizin hatékonyságát vizsgáltuk az aura nélküli migrén kezelésében török serdülőknél.
Módszerek – A vizsgálatba 46, aura nélküli migrénben szenvedő, napi 5 mg flunarizint kapó beteget vontunk be. Retrospektív vizsgálatunkban az esetek orvosi kartonját vizsgáltuk. A vizuális analóg skála (VAS) pontszámait és a MIDAS-pontszámokat hasonlítottuk össze a 3 hónapos kezelés hatékonyságának értékeléséhez.
Eredmények – Az átlagéletkor 14,37 ± 1,83 év volt. A betegek VAS- és MIDAS-pontszámai a harmadik hónap végére szignifikánsan javultak ($p < 0,05$). Mellékhatásokat a betegek 23,9%-ánál észleltek: a betegek 8,7%-ánál szedáció, 4,3%-ánál hangulatingadozás, 4,3%-ánál pedig hányás lépett fel. A betegek egyike sem hagyta abba a kezelést mellékhatás miatt.
Következtetés – Bár a migrén kutatásának és kezelésének fejlődése elkerülhetetlen, eredményeink alátámasztják, hogy a flunarizin továbbra is hatékony és tolerálható kezelési lehetőségnek tekinthető a serdülőkorú migréneseknél.

Kulcsszavak: migrén, flunarizin, MIDAS

Migraine is a common neurological issue in children and can lead to significant disability[1]. Its prevalence varies with age, ranging from 3% to 17%[2-3]. The incidence of headaches in childhood increases due to environmental factors. Children with limited access to outdoor play areas, resulting in a sedentary lifestyle, are at higher risk for developing headaches[4].

Flunarizine is a mixed sodium and calcium channel blocker that exerts its preventive effect in migraine, at least in part, by blocking P/Q-type channels in the brain. These P/Q-type calcium channels are presynaptic, high-voltage gated channels that contribute to vesicle release at synaptic terminals. Dysfunction of these channels has been implicated in various neurological disorders, including migraine[5].

Flunarizine was introduced in the 1980s for migraine treatment. Reports suggest that it may have protective effects against brain hypoxia by reducing intracellular calcium levels. Its impact on the overload and inhibitory effects on cranial artery contractility in animal models led to the investigation of its potential prophylactic role in migraine management. Flunarizine is recommended in various national treatment guidelines as a drug with level A evidence for migraine prophylaxis, at doses of 5–10 mg[6–8].

Various medications are used for migraine prophylaxis in children. These include antidepressants (e.g. amitriptyline), antiepileptics (e.g. topiramate, gabapentin) and calcium channel blockers (e.g. flunarizine)[9, 10]. Practice guidelines set a "benchmark" for evaluating the effectiveness of preventive treatment, such as a 50% reduction in headache frequency. The Childhood and Adolescent Migraine Prevention (CHAMP) trial, the largest comparative effectiveness study to date for preventive migraine treatment in children, showed interim results that amitriptyline and topiramate were not superior to placebo in reducing headache days. These findings have led to increased calls for pediatric headache specialists to prioritize behavioral approaches in preventive treatment[10, 11].

Published studies on flunarizine predate the recent endpoints suggested for evaluating migraine prophylactic drugs, meaning there is insufficient evaluation based on these newer criteria. Additionally, large-scale contemporary studies could provide valuable insights into re-evaluating flunarizine's efficacy in migraine treatment and its potential benefits[12].

The aim of this study was to evaluate the efficacy and tolerability of flunarizine in adolescent migraine headaches.

Materials and methods

This retrospective observational study was approved by the ethics committee of the University of KTO Karatay, Konya, Türkiye, (Study Protocol Number: 2024/050) and was performed in accordance with the Declaration of Helsinki. Written, informed consent was obtained from all participants' parents.

Patients with migraine without aura who were admitted to the tertiary neurology clinic for 24 months from May 1, 2022, to May 1, 2024, were enrolled in the study. Demographic and clinical features, chronic diseases were recorded.

ABBREVIATIONS

FIP: Flunarizine-Induced Parkinsonism
MIDAS: Migraine Disability Assessment Scale
NPRS: Numeric Pain Rating Scale
VAS: Visual Analog Scale

Participants

In our study, we retrospectively assessed the clinical characteristics of 46 adolescents who were diagnosed with migraine without aura and treated at the Neurology Clinic. The patients included in the study were diagnosed according to the *International Classification of Headache Disorders, 3rd Edition (ICHD-3)* diagnostic criteria used for the diagnosis of auraless migraine in children. Patients had pain complaints for at least 3 months. They had not used prophylactic treatment before. Patients had analgesic use for acute treatments but did not have medication-overuse headache.

ICHD-3 was published in 2018 and describes in detail the diagnostic criteria for types of headache in both adult and pediatric populations. The criteria for the diagnosis of migraine in children are described in ICHD-3 under the heading "Migraine Without Aura (1.1)"[13].

The medical records of adolescents diagnosed with migraine without aura and treated with flunarizine were reviewed. The Visual Analog Scale (VAS) and Migraine Disability Assessment Scale (MIDAS) values at the time of initial flunarizine administration were recorded, as well as the values after three months of treatment.

Instruments

The Visual Analog Scale

VAS is used to quantify certain parameters that are not easily measured numerically. It consists of a 10 cm line with two ends representing the extremes of the parameter being evaluated. Patients are asked to indicate their current state by drawing a line, placing a dot, or marking the point that best represents their condition. For example, for pain, one end of the line represents "no pain", and the other end

represents "severe pain". The length from the "no pain" mark to the patient's mark indicates the level of pain[14, 15].

The Migraine Disability Assessment Scale

MIDAS is a commonly used tool designed to measure disability associated with migraines. It assesses migraine-related disability over the previous three months. Studies in our country have shown that MIDAS is a reliable scale for measuring disease severity and determining treatment strategies in migraine patients. MIDAS evaluates the impact of headaches on the patient's life through five questions, focusing on the severity and frequency of the pain, as well as its impact on the patient's work, school, or home life. It is graded on a four-level scale: a score of 0–5 indicates minimal disability (grade 1), 6–10 indicates mild disability (grade 2), 11–20 indicates moderate disability (grade 3), and 21 or above indicates severe disability (grade 4)[16]. The Turkish validity and reliability study of it was conducted in 2004 by *Ertaş M* et al[17]. The MIDAS was used because the patients participating in the study were between the ages of 11-18 and the Turkish validity and reliability test of the Pediatric MIDAS had not been conducted.

Table 1. *Comparison of mean VAS and MIDAS scores at baseline and after 3 months of treatment*

Metric	Baseline Mean ± SD	3-Month Mean ± SD	p-value
VAS (Visual Analog Scale)	7.087 ± 0.96	5.06 ± 1.83	0.00
MIDAS (Migraine Disability Assessment Scale)	11.37 ± 4.32	8.13 ± 4.68	0.00

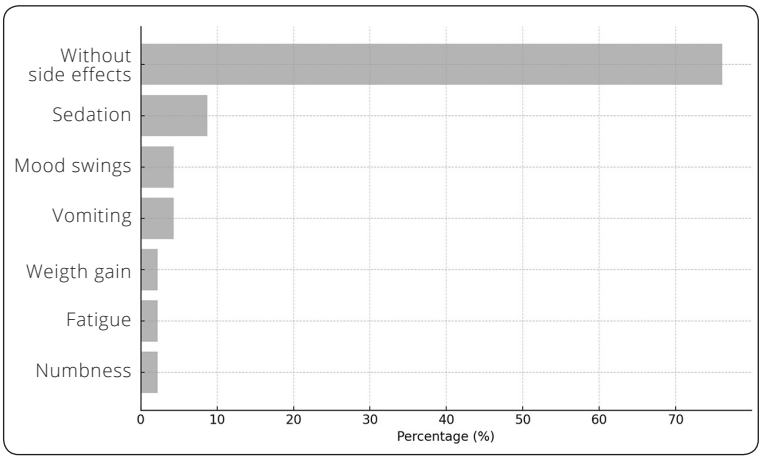

Figure 1. *Side effects of flunarizine over 3-month period*

Statistical analysis

SPSS 22.0 software was used for data analysis and $p < 0.05$ was accepted as statistical significance. Statistical analyses were performed using Chi-square, Mann-Whitney U, and Kruskal-Wallis tests.

Results

The age range of the patients was 11-17 years, the mean age was 14.37±1.83 years, 36 (78.3%) were female.

There was a significant improvement in the VAS and MIDAS scores of the patients at the end of the third month (p-values respectively: 0.00, 0.00) **(Table 1)**. Although the flunarizine caused a significant change in the VAS and MIDAS scores, there was no change in the MIDAS value of 14 patients in the study. **Figure 1** depicts the side effects of flunarizine use over the 3-month period. None of the patients discontinued the treatment due to side effects.

Discussion

The purpose of this study was to evaluate the efficacy of flunarizine in adolescents with migraine without aura and to detect its side effect profile and the reasons for discontinuation. At the end of three months of treatment with flunarizine for migraine without aura in adolescents, there was a significant improvement in patients' VAS and MIDAS scores. However, no benefit was observed in a portion of the patients. While the most common side effects were sedation, mood changes, and vomiting, no patient discontinued treatment due to side effects.

In a retrospective, single-center study focusing on the safety and efficacy of flunarizine use in childhood migraine prophylaxis[18], side effects were reported in 57% (41/72) of individuals. Although the effectiveness of flunarizine was similar to our findings, 18% of the participants in that study discontinued the medication due to side effects.

In an 8 months, double-blind, placebo-controlled, crossover study[19] evaluating the efficacy of flunarizine in migraine prophylaxis, which included 63 children, flunarizine was found to significantly reduce the frequency and average duration of headache attacks. One child discontinued the treatment due to excessive daytime sleepiness. The main side effects were daytime sleepiness and weight gain. This study also concluded that flunarizine is an effective drug for treating childhood migraine, with no serious side effects observed during the study period.

Another study reported a 50% reduction in headaches in 86.3% of patients by the third month of flunarizine use[20]. In this study, flunarizine was given as the first choice for all patients, suggesting that it could be an effective treatment for headache management due to its accessibility and treatment adherence. However, this study did not specify whether there was a decrease in the severity or frequency of pain or in which parameters pain decreased.

In our study, in accordance with the literature some of the patients did not benefit from flunarazine treatment. No change in MIDAS values was observed in this patient group. Since flunarizine is a drug that inhibits voltage-dependent calcium channels, mutations and variations affecting the functioning of these channels may be the reason for this[21].

In recent years, there have been concerns regarding the potential of flunarizine to cause parkinsonism in adults. In one study comparing patients who used flunarizine with those who did not[22], it was found that although the risk was low, it was higher in the flunarizine group. This study highlighted that Flunarizine-Induced Parkinsonism (FIP) may be associated with advanced age, a history of comorbidities, high-dose exposure, and long-term use. None of the participants of the current study had symptoms of parkinsonism.

There have been no studies on flunarazine-associated parkinsonism in children and adolescents. However, in one study, it was reported that a mutation in the ATP1A3 gene encoding the a3 subunit of the sodium-potassium ATPase caused rapid onset dystonia-parkinsonism (RDP) in a 13-year-old patient, which completely resolved with flunarazine treatment[23].

Nevertheless, flunarizine remains the most commonly used migraine prophylaxis medication in adults. A study utilizing South Korea's national insurance database, which comprehensively evaluated real-world treatment patterns covering nearly all treatment regimens, assessed 761,350 migraine patients and found that flunarizine was the most frequently used prophylactic drug at 36.89%[24]. We believe that evaluating its efficacy, along with documenting the adverse effects in adolescent, will contribute to the medical literature and provide valuable insights for reviewing the use of flunarizine.

This study was a retrospective, observational study conducted in a highly specific group of individuals, so the conclusions that can be drawn from the data are limited. However, it provides valuable insights into this rare group.

In conclusion, this study found that flunarizine was effective in reducing the frequency and severity of migraine attacks in adolescents. However, in a subset of patients, no effect was observed. Although mild side effects such as sedation and mood changes were seen in some patients, none of them discontinued the medication for this reason. The new generation of migraine medications, CGRP antagonists, have generally been developed for use in adults, and there is limited data on their use in adolescents. Research on the safety and efficacy of CGRP antagonists in adolescent migraine treatment is still insufficient.

Based on the results of our study and a review of the literature, flunarizine appears to be an effective treatment for pediatric patients, though it is important to limit the duration of treatment to ensure both efficacy and safety.

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CONFLICT OF INTEREST – The authors have no conflicts of interest to declare.

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