Acute Treatment of Migraine

Migren Akut Tedavisi

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Abstract

Migraine is one of the most frequent disabling neurological conditions with a major impact on the patient's quality of life. Migraine has been described as a chronic disorder that characterized with attacks. Attacks are characterized by moderate-severe, often unilateral, pulsating headache attacks, typically lasting 4 to 72 hours. Migraine remains underdiagnosed and undertreated despite advances in the understanding of its pathophysiology. This article reviews management of migraine acute pharmacological treatment. Currently, for the acute treatment of migraine attacks, non-steroidal anti-inflammatory drugs (NSAIDs) and triptans (serotonin 5HT_{1B/1D} receptor agonists) are recommended. Before intake of NSAID and triptans, metoclopramide or domperidone is useful. In very severe attacks, subcutaneous sumatriptan is first choice. The patient should be treated early in the attack, use an adequate dose and formulation of a medication. Ideally, acute therapy should be restricted to no more than 2 to 3 days per week to avoid medication overuse. (*Archives of Neuropsychiatry* 2013; 50 Supplement 1: S26-S29)

Key words: Migraine, acute, attack, treatment

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Özet

Migren, hastaların yaşam kalitesi üzerinde önemli bir etkiye sahip sık rastlanan nörolojik durumlardan biridir. Ataklarla karakterize kronik bir hastalık olarak tanımlanır. Ataklar genellikle 4 ile 72 saat süren, orta ya da şiddetli, genellikle tek taraflı, zonklayıcı baş ağrısı ile karakterizedir. Migren patofizyolojisinin daha iyi anlaşılmasına rağmen, tanınması ve tedavisi hala yeterli değildir. Bu makalede migrende akut farmakolojik tedavi yaklaşımı gözden geçirilmiştir. Günümüzde, migren ataklarının akut tedavisi için, non-steroid antiinflamatuar ilaç (NSAİİ) ve triptanlar (serotonin 5HT_{1B/1D} reseptör agonistleri) önerilir. NSAİİ ve triptan alımından önce, metoklopramid veya domperidonun verilmesi faydalıdır. Çok şiddetli ataklarda subkutan sumatriptan ilk seçenektir. Hasta, yeterli dozda ve formülasyonda bir ilaç ile atağın erken döneminde tedavi edilmelidir. İdeal olarak, ilaç aşırısı kullanımını önlemek için akut tedavi haftada en fazla 2-3 gün ile sınırlandırılmalıdır. (*Nöropsikiyatri Arşivi* 2013; 50 Özel Sayı 1: S26-S29)

Anahtar kelimeler: Migren, akut, atak, tedavi

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Migraine is a chronic neurological syndrome characterized with attacks which frequently causes to disability and is observed commonly in the community. Its diagnostic criteria were defined by the International Headache Society (IHS) (1). While it affects 15% of the adults in Europe and 12% of the adults in America, its lifelong prevalence in Turkey is between 12.5% and 19.9%. It is observed with a 2-3-fold higher rate in women probably due to genetic factors and fluctuating estrogen levels (2, 3, 4, 5, 6). Migraine is a

disorder affecting the brain from the meninges to the cortex and a great part of the brain stem. The trigeminovascular system plays a significant role in the pathophysiology. Many neurotransmitters including mainly serotonin, calcitonin gene-related peptide (CGRP), glutamate and proinflammatory cytokines (interleukin 1 and 6) are involved in the pathophysiology of migraine. Pathophysiology and thus clinical characteristics may show variance from person to person and between attacks in the same person. Therefore, acute treatment should be planned individually and even specifically for the attack.

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Many large placebo-controlled studies related with acute treatment of migraine have been published. In most studies, successful treatment of migraine attacks has been defined as elimination of pain completely 2 hours after treatment or transformation of moderate-severe pain to mild pain, efficiency of appropriate treatment in 2 of 3 attacks and absence of recurrence of headache and absence of use of drugs in 24 hours after a successful treatment. Currently, the most commonly used drugs in treatment of acute migraine attacks can be examined in two main groups as non-migraine-specific drugs (antiemetics, simple analgesics, non-steroid anti-inflammatory drugs (NSAI), combined analgesics, opioids) and migraine-specific drugs (ergot derivatives and triptans) (7, 8, 9, 10).

Non-Migraine-Specific Drugs

Antiemetics

Dopamin D2 receptor antagonists are used alone or in combination with other acute treatment drugs to treat headache and related nausea in migraine. Although there is no randomized controlled study on this subject, use of antiemetics is recommended to prevent nausea and possible vomiting during migraine attack and to increase absorption and bioavailability of analgesics and triptans used afterwards. When metoclopramide is administered orally, it has a mild analgesic action. When it is administered intravenously, it has a higher analgesic action. 10-20 mg metoclopramide is recommended in adults. 10 mg domperidon is recommended in adults and children because of possible extrapyramidal side effects of metoclopramide. Especially in patients with nausea, initiating acute attack treatment with antiemetics which are known to be efficient also in the prodromal period and which are known to prevent progression of migraine attack and completing treatment with migraine-specific or non-migraine-specific drugs will be an appropriate approach (11, 12, 13, 14, 15).

Analgesics

The first-line drugs in treatment of mild or moderate migraine attacks are analgesics. The analgesics which have been shown to be efficient in migraine include acetylsalicylic acid (ASA) (500-1000 mg), ibuprofen (200-800 mg), diclofenac (50-100 mg), etodolac (400-800 mg), paracetamol (1000 mg), metamizol (1000 mg) and tofenamic acid (200 mg) and fenazon (1000 mg) which are not present in the market in our country (16, 17, 18, 19, 20, 21, 22, 23, 24). In addition, it was shown that combinations of ASA, paracetamol and caffeine were more efficient compared to use of these substances alone or without caffeine (25). However, it should be kept in mind that combined preparations carry a higher risk in terms of medication overuse headache. Use of simple analgesics should be limited to 15 days a month and use of combined analgesics should be limited to 10 days a month to prevent medication overuse headache.

Opioids

The efficiency of opioid in treatment of acute migraine is minimal and there are no controlled studies. The most important indications include ischemic heart disease where migraine-specific drugs can not be used and patients who do not respond to other nonspecific drugs. Although they are used more frequently in other countries, they are used in patients who do not respond to other acute treatment drugs and rarely in our country.

Migraine-Specific Drugs

Ergot Alkaloids

Although migraine-specific, more selective and drugs with fewer side effects have been introduced, use of ergot preparations continues in treatment of acute migraine. The agonist action of ergot alkaloids on serotonin receptors is less specific compared to triptans and they have more side effects. Basically, their side effects in vasoconstrictive nature and nausea limit their usage. There are very few placebo-controlled randomized studies related with the efficiency of ergot alkaloids in acute treatment of migraine. In comparative studies, triptans were shown to be more efficient (26, 27, 28). Among ergot alkaloids, dihydroergotamine which is not found in our country has advantages in acute treatment of migraine with intravenous, intramuscular, subcutaneous and nasal administration opportunities, long half-life and low risk of medication overuse headache. Ergotamine tartrate which is another ergot preparation is available in our country as tablets containing combination of ergotamine tartrate and caffeine. Although its inexpensiveness is an important advantage, ergotamine tartrate should not be used in acute treatment of migraine because of its systemic vascular side effects and because of leading to medication overuse headache. Their use should be limited to young patients who do not respond to other acute treatment drugs with very rare attacks (29).

Triptans

5-HT (serotonin) 1B/1D receptor agonists called as triptanlar (sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan and frovatriptan (according to the order of release to the market)) are migraine-specific drugs. They should not be used in other headaches other than cluster headache. Although the exact mechanism of action of triptans is not known, they are thought to act by way of three basic mechanisms including vasoconstriction in the intracranial vessels (5-HT 1D), peripheral neuronal inhibition (5-HT 1B) and presynaptic dorsal root stimulation (5-HT 1D). In addition they may act on descending inhibitor pain pathways and on function of 5-HT 1F receptors. Discovery of triptans ushered a new age in acute treatment of migraine. Currently, they are still the main drugs in acute treatment of migraine. The efficiency of all triptans have been proved in large placebo-controlled studies and they have been shown to be the most efficient drugs developed so far (30, 31). Triptans were efficient in 60% of the patients who did not respond to NSAID drugs (32). They can be used as first-line drugs in patients who do not respond to non-migraine-specific drugs or in very severe attacks. 6 of 7 members of triptans except for almotriptan are available also in our country and they are used in acute treatment of migraine. The subcutaneous form of sumatriptan which is the firstly-developed member of this group is currently the gold standard in migraine treatment. Its action begins in a short time like 10 minutes. When administered at equivalent doses, oral sumatriptan, eletriptan, zolmitriptan, almotriptan and rizatriptan have similar efficiencies, but there are small differences between triptans. While the action begins in 30 minutes with oral rizatriptan and eletriptan, this time period is 45-60 minutes for oral sumatriptan, almotriptan and zolmitriptan (30).

The action of naratriptan and frovatriptan starts in approximately 4 hours (30, 33, 34). Although frovatriptan and naratriptan have lower efficiency, they should be preferred in patients who suffer from the side effects of triptan to a great extent, who have long attack times and high recurrence rates, since these molecules cause to fewer side effects and have lower recurrence rates and a long elimination half-life. Oral soluble tablets of rizatriptan and zolmitriptan may be preferred because of easy intake, though their efficiencies are not different compared to standard tablets. Zolmitriptan and sumatriptan are triptans which have nasal formulations. In our country, only sumatriptan nasal spray is available on the market. Nasal formulations act bypassing the gastrointestinal system like injectable formulations. These formulations may be preferred especially in patients who have vomiting or severe nausea in cases where subcutaneous sumatriptan can not be used. Although triptans can always be efficient during migraine attack, there is evidence that they are more efficient if they are taken in the early period (35, 36, 37). However, insisting that triptans be taken in the early period may lead to frequent drug use in some patients. IHS criteria limited triptan usage to 9 days a month maximally. Epidemiological studies showed that the risk of chronicity became significant with use of triptans for 12 days a month (38). Otherwise, development of medication overuse headache is possible with all triptans (29, 39, 40). A typical problem in treatment of attack in migraine is recurrence of headache which is defined as worsening of pain in 24 hours after transformation to painless state or to mild pain has been provided with medication. Recurrence occurs in approximately 15-40% of the patients who receive oral triptan (41, 42). If the first dose of a triptan is not efficient, the second dose is useless and should not be used. Triptans are usually well tolerated and cause to severe side effects rarely. Their use is contraindicated in presence of obstructive vascular disease (coronary artery disease, ischemic stroke) and uncontrolled hypertension and during pregnancy and lactation. Although no specific severe side effect has been reported, triptans should not be taken during aura in terms of safety. If they are taken during aura, they are inefficient. The best time of usage is the time of onset of headache. Efficiency decreases, when used in the late period especially in patients in whom allodynia develops (43, 44).

Triptans can be combined with antiemetics and NSAID drugs. Addition of a NSAID to triptans improves treatment response and decreases recurrence of headache. This was confirmed with use of combined tablet of naproxen sodium and sumatriptan (45). Although combined tablets are not available in our country, similar results may be obtained by using NSAID and triptan tablets simultaneously in patients with migraine in whom a better response is wished, when sufficient efficiency can not be provided alone. It may be appropriate to add an antiemetic drug to this treatment.

The basic principles of acute treatment of migraine include use of appropriate drug at the appropriate dose in the early period of headache, limiting acute treatment drugs to 2 days a week or 9 days a month, adding an antiemetic and/or preferring parenteral medication in patients who initially have nausea and vomiting or severe pain and assessment of side effect profile when selecting drugs. Some patients may respond to one drug, while they do not respond to another. Before changing the drug its efficiency should be assessed in at least two attacks. The best approach is planning treatment which can render the patient fully functional in 2 hours according to the severity of each attack in a stratified fashion. The ideal acute treatment drug acts rapidly, returns the patient

to normal function in a short time, is reliable, can be administered easily and has few side effects.

In summary, it is appropriate to use NSAID drugs or triptans according to the characteristics of the attack and patient following administration of metoclopramide or domperidon for acute treatment of migraine attacks. Subcutaneous sumatriptan is the first option in very severe attacks, in patients with vomiting and/or in cases where pain is wished to be eliminated in a short time.

Response to acute treatment drugs given at the appropriate time and doses is usually well in patients with migraine. If no success can be achieved in acute treatment, the following topics should be reviewed after assuring the diagnosis of migraine:

1. The dose of the drug used should be reviewed. If the dose is low, it should be increased. Analgesics may need to be used at higher doses in migraine attacks. Some patients may give better response to migraine –specific drugs at higher doses.

2. If the dose of the drug used is sufficient, the drug should be switched. A patient who does not respond to a NSAID, may give response to another NSAID. Similarly, a patient who does not respond to a triptan may give response to another triptan.

3. The formulation of the drug may be changed. If the patient is taking oral tablets, nasal or subcutaneous formulations may be tried. Especially in patients with nausea, an antiemetic may be added to treatment.

4. Combined treatment should be tried, if response to a single drug is not well (like adding NSAID to triptan).

5. It should be checked if the treatment drug is taken in the early period of attack when headache is mild.

6. It should be checked if there is overuse of caffeine or other acute migraine treatment drugs.

7. Initiating prophylactic treatment should be considered. Patients who have not responded to an acute treatment drug previously, may give response to the same drug after prophylactic treatment is started.

8. It should be checked if there is usage of other drugs causing headache (including nitroglycerine)

Studies related with development of new acute migraine treatment drugs are continuing. In the future, the aim of acute migraine treatment drugs will be to find molecules which are more specific to migraine, which have fewer side effects (especially fewer vascular side effects), which can be administered easily and which are readily available. Studies related with CGRP antagonists the results of which have been waited with great hopes have been terminated because of hepatotoxicity. Studies related with new serotonin receptor agonists (especially which act on 1F receptor), AMPA/Kainate receptor antagonists, orexins, nitric oxide, prostanoids, COX-1/COX-2 inhibitors and new formulations of diclofenac potassium, sumatriptan and dihydroergotamine are continuing (46).

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