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Review / Derleme

The Acute Treatment of Migraine Attack in Adults and American Headache Society Evidence Assessment of Migraine Pharmacotherapies

Erişkinlerde Akut Migren Atağının Tedavisi ve Amerikan Baş Ağrısı Derneği Migren Farmakoterapisi Kanıt Değerlendirmesi

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Summary

Migraine is a common, the primary debilitating and recurring headache disorder. The main purpose migraine acute pharmacology is to reduce the impact and disability caused by the attack of migraine. This review primarily reminds clinical pearls in acute treatment of migraine and also summarizes the American Headache Society Evidence Assessment of Migraine Pharmacotherapies that published last year.

Keywords: Migraine, attack treatment, migraine pharmacotherapies

Öz

Migren sık görülen, kısıtlılık yaratan ve tekrarlayıcı birincil baş ağrısı hastalığıdır. Migren atak tedavisinin temel amacı migren atağının etkisini ve yarattığı kısıtlılığı azaltmaktır. Bu gözden geçirme öncelikle migrenin akut tedavisindeki klinik tavsiyeleri hatırlatmakta ve geçen yıl yayınlanan Amerikan Baş Ağrısı Derneği Migren Farmakoterapisi'nde Kanıt Değerlendirmesi özetlenmektedir.

Anahtar Kelimeler: Migren, atak tedavisi, migren farmakoterapisi

Introduction

Migraine is a common disorder that is generally unilateral, becomes worse with physical activity, and is characterized by attacks associated with moderate-severe throbbing headache, nausea and/or vomiting, photophobia and phonophobia (1,2). Migraine is the 5th greatest cause of disability in women and among in the top twenty in men (3). The main aims of migraine pharmacotherapy are to decrease the number of attacks and the effect and disability they cause. It is estimated that approximately 97% of patients with migraine use drugs for acute treatment but only 13% receive preventitive treatment (4,5). The aims of this review were to remind physicians of the general approaches that are recommended for treatment of migraine attacks, and to summarize an evidence-based evaluation of acute migraine attack treatment, which was published this year by the American Headache Society (6).

The Aims of Acute Migraine Attack Treatment

The short-term aims of treatment for acute migraine attacks are to rapidly decrease pain, its associated symptoms disability; totally relieve pain within 2 hours; prevent recurrence of pain within 24 hours; prevent the need for salvage treatments; and avoid any adverse effects. The long-term aims of migraine treatment are to avoid overuse of acute migraine treatments and decrease emergency department admissions.

The principles of acute migraine treatment are to treat pain immediately; limit treatment for attacks to a maximum 2 days a week; use the right dose and formulation; treat migraine attacks that are associated with nausea and vomiting from an early period, or migraine attacks associated with severe nausea and vomiting or awakening from sleep or rapidly progressing migraine attacks with parenteral treatments; and to take into account adverse effects of treatments.

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There are 3 phases of migraine without aura; activation of the central generator, triggering of peripheral pain mechanisms, and central spread of pain signals. Migraine is a state of neuronal hyperexcitability. After the activation of the central generator, two peripheral meningeal pain mechanisms are activated; neurogenic inflammation and vasodilation. Kinins released by neurogenic inflammation cause production of cyclooxygenase. Cyclooxygenases convert arachidonic acid to prostaglandins. Calcitonin gene-related peptide (CGRP) and prostaglandins cause vasodilatation at meningeal blood vessels and inflammation at peripheral tissues. Triptans and ergot preparations prevent CGRP release from serotonin receptors. Non-steroidal anti-inflammatory drugs (NSAID) terminate the arachidonic acid cascade. Thereby, peripheral pain mechanisms may be stopped by standard acute treatments. In the third phase, pain signals are transmitted to the central nervous system from trigeminal nucleus caudalis. Ascending signals spread to the thalamus and cortex, affect more neurons, and also activate neighboring autonomic nuclei. This is known as central sensitization and is characterized clinically by allodynia. At the peak of the migraine attack, light (photophobia), sound (phonophobia), smell (osmophobia), and touch (cutaneous allodynia) are disturbed due to central sensitization. The aim of acute treatment is to prevent or reverse central sensitization, which can develop within 30 minutes of the start of a migraine attack. Therefore, the gold standard is to treat acute migraine attacks immediately with effective drug dose. However, patients who use painkillers for more than 10 days a month due to headache should be started on preventive treatment due to the risk of developing medication overuse headaches.

Specialized Attack Treatment for Patients

An effective approach to migraine attacks is to start with NSAID's and add a triptan in the absence of adequate response within an hour. Nevertheless, the identification of associated trigger factors for migraine attacks and analysis of disability, attack features, and successes and failures of previous treatments are important to achieve success. The choice of acute treatment should include a detailed interview with the patient and planning patient-specific treatment. The level of disability due to an attack is important for choosing an accurate treatment. Lipton et al. (7) rated migraine patients using the Migraine Disability Assessment Score (MIDAS). The critical question in MIDAS was "How many days in last 3 months was your work, home, or social activities impaired at least 50% due to migraine?" According to the MIDAS scores, 0-5 rated as little or no disability; 6-10 rated as mild disability; 11-20 rated as moderate disability; and 21+ rated as severe disability.

In one study, 3 strategies were selected for acute treatment. The first was a two-phased treatment for the patients in the first group. The first three migraine attacks of these patients were treated with metoclopramide, which is nonspecific for migraine. If the response after three attacks was insufficient, the patients proceeded to the zolmitriptan group, which is specific for migraine.

The second strategy was a 2-level treatment within an attack. These patients were treated with acetyl salicylic acid (ASA) and metoclopramide at the beginning of an attack, if their pain was not relieved within 2 hours they received zolmitriptan.

The third strategy used a group-based strategy. In this group, zolmitriptan was given to patients who had moderate to severe disability according to MIDAS and ASA at the beginning of an attack and metoclopramide was given to patients who had mild or no disability.

The third strategy was found to be superior to 2-phased strategies in pain relief and time of disability. In addition, post-hoc analysis showed that the group-based third strategy was less costly than others (8). In view of these findings, and taking into consideration the vascular contraindications, a specific or nonspecific treatment should be chosen at the first step according to the degree of disability.

What Should the Frequency of Acute Migraine Treatments be in a Month?

Patients frequently seek help when drugs used in acute treatment fail and disability due to migraine increases. Understanding unmet needs is the most important key to improving treatment. If the neurologist uses the same drug immediately at an early period and at an optimal dose recurrence, disability, need for salvage treatments, and risk of development of allodynia will be decreased. The frequency of a patient's headaches should be kept in mind during early intervention. The frequency of treatment for acute attacks should be limited to two per week. The American Migraine Prevalence and Prevention study showed that use of butalbital more than 5 times a month carried risk of migraine transformation (9). Use of opioids for more than 8 days a month, and even use of a single dose was detected to be associated with chronification. Therefore, butalbital and opioids should be avoided in the treatment of acute migraine attacks. Use of triptans for ≥10 days a month is associated with development of drug overuse headache. NSAIDs have biphasic effects; if they are used less than 5 days a month they prevent conversion to chronic migraine but if they are used for 10-15 days they increase risk.

Changing Acute Attack Treatment

Before changing a drug for acute treatment after deciding it is ineffective, at least 2 trials during attacks are recommended. If the drug fails to control headache despite its use during early period at an adequate dose its route of administration may be changed. Usually, parenteral, nasal or rectal formulations may be preferred over oral treatments, which are used at the first step. If the drug is still not effective, a different molecule from the same drug class (e.g. NSAIDs) may be chosen. If effective pain control still cannot be achieved, the acute treatment may be changed. This can be done in two ways. The first is to choose a drug from another class (e.g. triptans or ergo). The second is a combination treatment; for example sumatriptan 85 mg/naproxen sodium 500 mg (not present in our country) or simply an NSAID with an ergot or triptan may be used. Moreover, the addition of dopamine agonists to these drugs produces a synergistic effect.

Acute Treatment in Cases with Vascular Disease

Naproxen sodium, which lacks cardiotoxicity, may be preferred in patients without renal or gastrointestinal contraindications (10). Other choices include antidopaminergic, antihistaminic,

antiepileptic drugs, or baclofen. The presence of a vascular disease does not permit the choice of opioids or butalbital in the treatment of acute migraine attack, because these drugs carry risk for conversion to chronic forms of migraine and therefore they should be avoided.

The American Headache Society Evaluation of Evidence Base in Migraine Pharmacotherapy

The American Academy of Neurology (AAN) summarized the evidence base for effectiveness of acute migraine drugs in a guideline published in 2000 (11). In a review this year, members of the American Headache Society guideline section updated an evidence evaluation for acute treatment of migraine attacks (6). The authors scanned publications about treatment of acute migraine attacks between 1998 and 2013, followed the methods of guideline development by AAN development, evaluated every abstract, and determined whether the quality of the article was adequate for their review. In the first scan, 805 articles were found and 132 were selected for review. Two referees then evaluated evidence levels of all articles. Each article was rated from 1 to 4 according to the treatment classification of the AAN guideline. Evidence level 1 defined well planned, double-blind, randomized, placebo-controlled studies, and evidence level 4 defined retrospective studies with uncertain results or case presentations. The evidence level for each drug according to quality of research was;

Level A: Effectiveness (or ineffectiveness) in acute migraine has been shown with at least two class 1 studies,

Level B: Effectiveness (or ineffectiveness) for acute migraine was supported by one class 1 study or by two class 2 studies,

Level C: Possible effectiveness (or ineffectiveness) for acute migraine was supported by one class 2 study or two class 3 studies,

Level U: Evidence level was inadequate or too controversial to support or reject use of this drug for acute migraine treatment.

From the older review published in 2000, no class 1 or class 2 study was found for butorphanol (intramuscular or nasal spray), butalbital/aspirin/caffeine or butalbital/aspirin/caffeine/codeine, acetaminophen /codeine, dihydroergotamine (DHE) (nasal spray, intrasmuscular, intravenous), flurbiprofen, hydrocortisone, isomethepten, intranasal lidocaine, or meperidine. To date, no new class 1 or 2 studies have been found to support the use of intravenous diphenhydramine, intravenous valproate, intravenous verapamil, oral tolfenamic acid, or celecoxib. Table 1 summarizes the evidence strength of drugs used in acute migraine treatment (6).

Recommendations and Discouragements of the American Headache Society Evidence Evaluation for Migraine Pharmacotherapy

In the discussion section, the authors stated that their systematic review of current publications rated evidence strength for each drug but did not provide guidance for the selection of treatment for individual patients. In clinical practice, acute treatment may cause serious adverse effects due to tolerance and dependence from barbiturates or opioids, peptic ulcers or renal disease as a result of NSAIDs, or worsening of migraine because of medication overuse headaches. Classification of drugs and the presence of level A evidence for effectiveness of drugs in acute migraine treatment does not mean that these drugs should be the first-line treatments. For example butorfanol, an opioid analgesic, is frequently avoided because of the risks of dependency and medication overuse headaches, despite the fact that there is strong evidence showing its superiority to placebo.

In this evaluation report, the evidence of strength was based on the drug's superiority against placebo; comparisons between drugs were not performed. To do this, head-to-head studies that compare drugs or careful meta-analyses are required. Moreover, study designs vary according to inclusion and exclusion criteria (e.g. migraine phenotype, frequency; special medical conditions of excluded patients; allowance of prophylactic treatments for migraine; inclusion of patients whose previous migraine treatments failed), number of treated attacks, time of initiation of acute treatment (e.g. whether the severity of attack was mild, moderate or severe; early or late after start of the migraine attack) and measurements of response. Although primary outcome criteria vary, the most commonly used ones are painless state 2 hours after treatment initiation and staying painless for 2 hours. The other primary outcome criteria were change in visual analogue scale before and after treatment, painless time period, painless period for 24 hours, and painless period for 4 hours. Secondary criteria also vary, but usually the criteria used for improvement of headache are nausea, photophobia, phonophobia, and improvement of disability. Staying headache-free and persistence of this state are criteria that are more difficult to be achieved than relief of headache for 2 hours. Therefore, studies with higher percentages of patients use '2 hours relief from headache' as a primary outcome measure. The International Headache Society Clinical Study Guideline, which was published in 2012, accepts headache-free state for 24-48 hours with relief in other migraine symptoms as "ideal migraine treatment response" (12). However, in acute treatment studies, it recommends use of "percentage of patients that stay headache-free for 2 hours."

This review does not include acute migraine treatment in children or the elderly. The studies included in this review evaluated the effectiveness of drugs for acute migraine attack in adults with migraine attacks with or without aura. However, the efficacy of drugs in status migrainosus, chronic migraine or menstrual migraine were not evaluated. Moreover, patients with severe migraine were excluded in some studies. Therefore, before consulting the information in this review, the individual characteristics of each patient and their migraine attack should be considered.

Conclusion

According to a systematic review of publications and rating of evidence strength, some drugs in the following classes were found to be effective in acute migraine treatment: Triptans, ergotamine derivatives, NSAID's, opioids, and drug combinations. Many other drugs were evaluated as probably effective or possibly effective. This evidence-based review for drug efficiency recommends that possible drug adverse effects, reactions that may develop, drug-drug interactions, and contraindications of the patient should be considered when deciding which drug will be prescribed for migraine attack treatment.

Table 1. Evidence strengths of drugs used for acute migraine treatment
Level A
Analgesic: Acetaminophen 1.000 mg (for attacks without disability)
Ergots: DHE *nasal spray 2 mg, pulmonary inhaler 1 mg
NSAIDs: *Aspirin 500 mg; Diclofenac 50-100 mg; Ibuprofen 200-400 mg; *Naproxen 500-550 mg
Opioid: *Butorfanol nasal spray 1 mg
Triptans: Almotriptan 12.5 mg; Eletriptan 20 mg-40 mg-80 mg; Frovatriptan 2.5 mg; *Naratriptan 1-2.5 mg; *Rizatriptan 5-10 mg; Sumatriptan *oral 25 mg-50 mg-100 mg, *nasal spray 10-20 mg, patch 6.5 mg, *SC 4-6 mg; Zolmitriptan nasal spray 2.5-5 mg, *oral 2.5-5 mg
Combinations: *Acetaminophen/aspirin/caffeine 500/500/130 mg; sumatriptan/naproxen 85/500 mg
Level B
Antiemetic: *Chlorpromazine IV 12.5 mg; Droperidol IV 2.75 mg; *Metoclopramide IV 10 mg; *Prochlorperazine IV/IM 10 mg, PR 25 mg
Ergots: DHE *IV, IM, SC 1 mg; *Ergotamine/caffeine 1/100 mg
NSAID's: *Flurbiprofen 100 mg; Ketoprofen 100 mg; Ketorolac IV/IM 30-60 mg
Others: MgSO4 IV (migraine with aura); *Isometheptene 65 mg
Combinations: *Codeine/acetaminophen 25/400 mg; Tramadol/acetaminophen 75/650 mg
Level C
Antiepileptic: Valproate IV 400-1.000 mg
Ergot: *Ergotamine 1-2 mg
NSAID's: Phenazone 1.000 mg
Opioids: *Butorfanol IM 2 mg; *Codeine 30 mg PO; *Meperidine IM 75 mg; *Methadone IM 10 mg; *Tramadol IV 100 mg
Steroids: Dexamethasone IV 4-16 mg
Others: *Butalbital 50 mg; *Lidocaine intranasal
Combinations: *Butalbital/acetaminophen/caffeine/codeine 50/325/40/30 mg; *Butalbital/acetaminophen/caffeine 50/325/40 mg
Level U
NSAIDs: Celecoxibe 400 mg
Others: *Lidocaine IV; *Hydrocortisone IV 50 mg
Others
Level B negative: Other: octreotide SC 100 πg
Level C negative: Antiemetics: *Chlorpromazine IM 1 mg/kg; *Granisetron IV 40 mg-80 πg/kg
NSAIDs: Ketorolac tromethamine nasal spray
Analgesic: Acetaminophen IV 1.000 mg
DHE: Dihydroergotamine, NSAIDs: Non-steroidal anti-inflammatory drugs, IV: Intravenous, IM: Intramuscular, PO: Phosphate, SC: Subcutaneous, *Based on evidence review by the American Academy of Neurology in 2000

Ethics

Peer-review: Externally peer-reviewed.

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