Medication Overuse Headache: The Reason of Headache That Common and Preventable

İlaç Aşırı Kullanımı Baş ağrısı: Sık ve Önlenebilir Bir Baş ağrısı Nedeni

Elif KOCASOY ORHAN, Betül BAYKAN

Istanbul University, Istanbul Medical Faculty, Department of Neurolog, Istanbul, Turkey

ABSTRACT

Medication overuse headache (MOH) is well-defined clinically and is one of the common reasons of chronic daily headache, but its pathophysiology has not been elucidated yet. MOH has varying clinical features in regard to regional, psychosocial, medical and economic factors. Even though, the studies have shown that many factors may play a role, MOH is likely to occur in patients who are prone to primary headaches. Mainstay of the treatment is to withdraw the excessively used analgesic drugs. The primary prevention with education of the patients as well as early diagnosis and treatment of MOH will reduce its increasing financial burden on both patients and countries. Meticulous and multifactorial evaluation of the disease besides the diagnosis and treatment of the comorbid diseases will reduce the risk of recurrences. (*Archives of Neuropsychiatry* 2013; 50 Supplement 1: S47-S51)

Key words: Headache, medication overuse headache, analgesics, detoxification, chronic daily headache

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ÖZET

İlaç aşırı kullanımı baş ağrısı (İAKB) klinik olarak iyi tanımlanmış olup kronik günlük baş ağrısının sık görülen nedenlerinden biridir ancak patofizyolojisi henüz bilinmemektedir. İAKB özellikleri bölgesel, psikososyal, medikal ve ekonomik faktörlere göre değişiklikler gösterebilmektedir. Çalışmalarda birçok faktörün rol oynayabileceği gösterilmekle birlikte, primer baş ağrısına yatkın olan kişilerde ortaya çıkmaktadır. Tedavinin temel taşı olarak kullanılan analjezik amaçlı ilaç veya ilaçların bırakılması oluşturur. Sıklığı giderek artan bu hasta grubunun en baştan eğitime engellenmesi yanı sıra tanınması, erken ve doğru tedavi edilmesi hem hasta hem de ülkelerin mali yükünü azaltacaktır. Hastalığın çok yönlü olarak ele alınması, komorbid hastalıkların tanınip tedavi edilmesi de nüks riskini azaltmak açısından önem taşır. (*Nöropsikiyatri Arşivi* 2013; 50 Özel Sayı 1: S47-S51)

Anahtar kelimeler: Baş ağrısı, ilaç aşırı kullanımı baş ağrısı, analjezikler, detoksifikasyon, kronik günlük baş ağrısı

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

Introduction

The ability of drugs used for the aim of analgesia to increase headache when used intensively is noted as a considerable interesting condition which is generally neglected, though known for long years and which should be paid great attention in patient education. Medication overuse headache (MOH) was examined in the subgroup of "headaches related with substance use or discontinuation" under the title of secondary headaches contained in the second part according to the headache classification of the International Headache Society (IHS) reviewed for the second time in 2004 (1). This type of headache which was previously named differently as "rebound headache", "headache induced by drugs" "headache triggered by drugs" or "medication abuse headache" was defined as an interaction between a therapeutical agent overused and a sensitive patient. The most common cause

of a picture of migraine-like headache more than 15 days a month or mixture of migraine and tension headache more than 15 days a month is overuse of migraine drugs and/or analgesics. Another important issue is the fact that the drugs used for treatment are received both frequently and regularly. According to the criteria defined, use of ergotamine, triptan, opioid and combined analgesics for 10 days a month or more and use of simple analgesics 15 days a month or more for a period longer than 3 months for changing/worsening headache is required (Table 1) (2).

In fact, MOH is a secondary chronic daily headache which is observed frequently. The patients who initially have a diagnosis of episodic migraine use analgesics frequently for headache and thus a critical threshold is reached and transformation to chronic daily headache occurs. Overuse of drugs develops a headache which initiates newly or worsens and becomes more frequent in these patients (3). Chronic tension headache is associated less

Correspondence Address/ Yazışma Adresi

Elif Kocasoy Orhan MD, Istanbul University, Istanbul Medical Faculty, Department of Neurolog, Istanbul, Turkey

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frequently with MOH. Especially in patients who refer to headache centers, transformation to a chronic headache occurs with overuse of analgesics. If chronic daily headache is thought as an umbrella, it covers primary or secondary daily headaches which last for longer than 4 hours including MOH. The triad of chronic headache, overuse of any drug for headache and worsening headache with this overuse which were reported as the general principles for MOH by International Headache Association should be always kept in mind.

Epidemiology

Epidemiological studies demonstrated that the prevalence of medication overuse accompanying chronic headache was 1-2% in the general population (4, 5, 6, 7, 8, 9, 10). In different countries including Brasil (6%) and Russia (10%), the prevalence of chronic headache and thus MOH was found to be higher (11, 12). This is explained by socioeconomical factors as well as genetic predisposition. In a study conducted with adults by house interviews, this rate was found to be 2.2% in women and 0.6% in men (13). Although MOH is generally observed more frequently in the middle age group and in women, it is being diagnosed even in adolescents currently. This increases the importance of the issue. MOH is observed in 4% of the patients presenting to neurology outpatient clinics in our country (14).

Use or overuse of analgesics and migraine drugs vary according to regional, psychosocial, medical and economical factors. The most commonly overused drugs in the whole world are simple analgesics (15, 16, 17). Overuse of triptan group of drugs is rarer and is observed more frequently in developed countries (12, 13, 18). In our country, simple analgesics are used most commonly in treatment of migraine with a rate of 19.3%, while triptans are used only with a rate of 2.9%. Again, in our country, MOH develops in 8.2% of the patients with migraine. MOH occurs in 4.8 % of the patients with migraine who use only simple analgesics, while this rate is 3.3% in patients who use ergotamine, analgesic and triptan combinations (13). Overuse of the ergotamine group which is still widely used in our country tends to decrease in the world.

Risk Factors and Pathophysiology

MOH is an interaction between a sensitive patient and the analgesic overused. It is thought that genetic predisposition also plays an important role in developing medication overuse headache in patients who have migraine of tension type headache. In patients who used analgesics at a high dose and for long periods for other conditions (for example: arthritis), an increase in the incidence of headache was not found. Interestingly, in this group, the patients who developed MOH were noted to have migraine previously (19, 20). In addition, in patients who have cluster type headache, MOH develops very rarely despite daily triptan use except for the patients with a familial history of migraine (21). The most important risk factor in development of MOH is overuse of drugs. Any kind of analgesic may lead to development of chronic headache. However, the reason of why this risk is higher with some drugs has not been elucidated yet. Population-based studies have shown that caffeine is moderately risky in terms of development of chronic headache (22). The risk of development of MOH increases with combined preparations containing caffeine.

The risk is also increased in comorbid psychiatric diseases including depression and anxiety (23, 24). Low socioeconomical status is also among risk factors. Especially in immigrant populations in European countries, the prevalence of both chronic headache and MOH was found to be high (25, 26). This was related with abuse of insufficient medical care. Other important conditions accompanying chronic headache include pains of other body parts including fibromyalgia, temporomandibular joint disease and back pain. It was shown that there was a bi-directional relation between chronic headache and musculoskeletal system (27).

The pathophysiology of MOH is not known yet (28). Although studies suggest that many factors are involved, MOH develops only in individuals who have a predisposition. Evidence suggesting that central sensitization has an important role in chronic headache gets stronger. In chronic migraine, chronic tension headache and MH, facilitation was shown with pain processing pathways of the trigeminal system by many psychophysical and electrophysiological techniques (29, 30). Changes at molecular level are also one of the possible mechanisms in MOH (31). Different mechanisms may be involved according to the drug used. Human and animal studies showed that glutaminergic and serotonergic system, dopamine and endocannabinoids had different tasks in pain modulation, cortical spreading and central sensitization (32).

Neuroimaging studies related with MOH are still continuing. Both neuroimaging and electrophysiological tests contribute to our understanding of neuronal circuits in MOH and localizing related brain areas. In a PET study, glucose metabolism was measured before and after discontinuation of the drug in migraine and MOH (33). Many brain areas related with pain were found to be hypometabolic, but it was observed that these areas rapidly showed activity with discontinuation of analgesics. Observation of metabolic changes in multiple areas was interpreted as a result of headache. However, in contrast to this observation, hypometabolism in the orbitofrontal cortex continued despite discontinuation of drugs and it was proposed that this might be related with recurrences in patients with MOH. It is known that the orbitofrontal cortex is hypometabolic also in drug abusers.

Treatment and Follow-up

MOH requires a multi-directional approach. In addition, it should be considered that it is a dynamical disorder and the recurrence rates are high as well as remission rates. In treatment, 4 basic rules should absolutely be applied. Firstly, the patient and family should be informed about this issue. It is known that patient compliance and success rates are high in therapies starting with patient education (34, 35). The cornerstone of treatment consists of discontinuation of the drug or drugs used. The patient may be followed up with frequent outpatient visits during this period or may be hospitalized, if necessary. It should be informed that symptoms including headache, nausea, vomiting, tachycardia, hypotension, nervousness, and strain may occur, but they are transient. It should be explained that withdrawal symptoms will be experienced most intensively in the first 2 weeks (2-10 days), but the patient should definitely not take analgesics despite all these symptoms. Studies showed that the withdrawal period was shorter in patients who only used triptan (36, 37). Rarely, seizures or hallucinations may

Tablo 1.

8.2 Medication Overuse Headache Diagnostic Criteria (ICHD-II revision recommendation) (adapted from the reference number 2)

A. Headache > 15 days/month

B. Overuse of one or more of symptomatic/acute treatment drugs regularly for longer than 3 months

1. Ergotamine, triptan, opioid or combined analgesics ≥ 10 days/month;

2. Use of simple analgesics or ergotamine, triptan, analgesics, opioids regularly for ≥ 15 days/month for a longer period of 3 months (no specific class)

C. Headache has developed or worsened markedly during medication overuse.

D. Headache improves or returns to the previous status in 2 months after the drug is discontinued

8.2.1 Ergotamine Overuse Headache

A. Headache meeting at least one of the following properties and the C and D criteria for >15 days a month:

1-Bilateral

2-Pressure/compressive character

3-Mild or moderate severity

B. Use of ergotamine regularly for 10 days or more a month for 3 months or longer

C. Headache has developed or worsened markedly during overuse of ergotamine

D. Headache disappears or returns to the previous status 2 months after ergotamine is discontinued

8.2.2 Triptan Overuse Headache

A. Headache meeting at least one of the following properties and the Cc and D criteria for >15 days a month:

1-Predominantly unilateral

2-Throbbing

3-Moderate or severe

4-Increase in headache with routine physical activities or headache causes avoidance of these activities (for example, walking or climbing up stairs)

5-At least one of the following accompanies:

a) Nausea and/or vomiting

b) Photophobia and phonophobia

B. Use of triptan regularly for 10 days or more a month for 3 months or longer

C. Headache has developed or worsened markedly during overuse of triptan

D. Headache disappears or returns to the previous status 2 months after triptan is discontinued

8.2.3 Analgesic Overuse Headache

A. Headache meeting at least one of the following properties and the C and D criteria for >15 days a month:

1-Bilateral,

2-Pressure/compressive (non-throbbing)

3-Mild or moderate severity

B. Use of simple analgesics regularly for 15 days or more a month for 3 months or longer

C. Headache has developed or worsened markedly during overuse of analgesics

D. Headache disappears or returns to the previous status 2 months after analgesics are discontinued

8.2.4 Opioid Overuse Headache

A. Headache should be present for >15 day a month and meet the C – D criteria:

B. Use of opioid for 10 days or more a month for longer than 3 months

C. Headache has developed or worsened markedly during overuse of opioid.

D. Headache disappears or returns to the previous status 2 months after opioid is discontinued

8.2.5 Combined Medication Overuse Headache

A. Headache with at least one of the following properties meeting the C and D criteria for >15 days a month:

1-Bilateral

2- Pressure/compressive (non-throbbing)

3-Mild or moderate severity

B. Use of combined preparations regularly for 10 days or month a month for longer than 3 months

C. Headache has developed or worsened markedly during overuse of combined preparations

D. Headache disappears or returns to the previous status 2 months after combined preparations are discontinued

occur in this period. Intake of plenty amount of fluid and rescue medication constitute the third foot of this treatment. In this period which is called detoxification, assistant/rescue drugs may be used to alleviate withdrawal symptoms. If necessary, antiemetics, analgesics, triptans, tranquilizers and neuroleptics may be used limitedly. Although there is no definite consensus, steroids may be used for a short time to eliminate withdrawal symptoms. However, in two placebo-controlled studies, the superiority of prednisolone given at a dose of 60-100 mg/day for 5 days to placebo could not be demonstrated (38, 39). There are no standard, generally accepted, evidence-based therapies in MOH. Assessment of the patient in a multi-directional fashion, pharmacological and psychodynamical approach and short-term psychotherapy may increase the success of treatment. The risk of recurrence may be tried to be decreased with treatment of accompanying psychiatric problems. Although preventive drug treatment in these patients is controversial, antidepressant including amitriptyline or antiepileptic drugs including valproic acid or topiramate may be utilized during clinical follow-up of the patients. In addition, recommendation of behavioral therapies and treatment of comorbid diseases should not be ignored (40).

The rate of recurrence during detoxification is high and depends on the type of headache and the time of regular usage of medication. If the initial headache is tension headache or tension headache accompanied by migrainous pain, the risk of recurrence in these patients is high. Recurrence is observed more frequently in patients who have been using regular medication for a long time. The risk of recurrence is lower in patients who use triptan compared to other patients. In long-term follow-ups lasting for 4-6 years, the rates of recurrence varies between 40% and 60% in different studies (41, 42, 43, 44, 45).

It is very important to select the right drug in patients with migraine, recommend the patients to avoid combined drugs as much as possible and administer early prophylactic treatment in migraine with appropriate drugs in order to prevent development of MOH. No guide related with the follow-up and treatment of MOH has been established yet and there are no uniform endpoints in studies performed (46). Among the endpoints which should be considered, the number of days with headache (day/month) seems to be more significant compared to the number of drugs taken. Recurrence and response rates (50% decrease in the frequency of headache) and headache index (frequency x severity) should be included in these endpoints.

Conclusively, MOH is a chronic headache which has a gradually increasing frequency, leads to disability and may cause to greater problems. Currently, it is the 3rd most common headache following migraine and tension type headache and its iatrogenic origin is important. Awareness of this disease is important especially in terms of prevention of its development and in terms of early diagnosis and treatment if it has developed. As with all chronic diseases, economic load of MOH for individuals and for countries increases gradually. Multi-directional consideration of the patients and treatment of comorbid diseases will both increase the chance of cure and decrease the risk of recurrence.

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