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OVERUSE OF SYMPTOMATIC MEDICATIONS AMONG CHRONIC (TRANSFORMED) MIGRAINE PATIENTS

Profile of drug consumption

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ABSTRACT - Chronic daily headache and chronic (transformed) migraine (TM) patients represent more than one third of the subjects seen in specialized headache centers. Most of these patients may overuse symptomatic medications (SM) taken on a daily basis to relieve headache and associated symptoms. The conversion to the daily or near-daily pattern of headache presentation is thought to be related to the medication overuse. The aim of this study was to evaluate the profile of SM consumption among transformed migraine patients attending a tertiary center. One hundred thirty three consecutive patients (22 men and 111 women, ages 17 to 80) with TM and overuse of SM according to the proposed criteria of Silberstein et al (1994, 1996) were prospectively studied. None of the patients were under treatment for other conditions. Among them, 73 (54.9%) were using one category of SM, while 55 (41.3%) and 5 (3.8%) patients were taking simultaneously two and three categories of SM respectively. The categories of overused symptomatic medications varied from simple analgesics to narcotics, triptans and combinations of ergot derivatives and caffeine and of analgesics and caffeine. The average intake per patient per day was of 3 to 4 tablets and mostly of the patients overused simple analgesics (isolated or in combination with other substances) (75.2%), caffeine containing drugs (71.4%), drugs containing ergotamine derivatives (26.1%), triptans (alone or combined) (15.5%), drugs with narcotics or ansiolitics (13%) and anti-inflammatory drugs (3.7%). The mechanisms by which the overuse of symptomatic medications may play a role in this transformation are uncertain but despite of the necessity of controlled trials to demonstrate the real role of such compounds in the development of transformed migraine, this study emphasizes the necessity for more rigorous prescribing guidelines for patients with frequent headaches.

KEY WORDS: chronic (transformed) migraine, overuse, symptomatic medications, analgesic rebound headache.

Uso excessivo de medicações sintomáticas em pacientes com migrânea crônica (transformada): perfil de consumo medicamentoso

RESUMO - Os pacientes com cefaléia crônica diária e migrânea crônica (transformada) (MT) representam mais de um terço dos pacientes vistos em centros especializados. Muitos destes pacientes abusam de medicações sintomáticas (MS) tomadas em caráter diário para aliviar a cefaléia e/ou os sintomas associados. A conversão para o padrão de apresentação diário ou quase diário parece ser relacionada ao uso excessivo de MS. O objetivo deste estudo foi avaliar o perfil de consumo de medicações sintomáticas em pacientes sendo atendidos em centro terciário de cefaléias. Cento e trinta e três pacientes (22 homens e 111 mulheres, com idades entre 17 e 80 anos) consecutivos preenchendo os critérios propostos por Silberstein e col. (1994, 1996) para MT e uso excessivo de MS foram estudados prospectivamente. Nenhum dos pacientes encontrava-se sob tratamento regular para outras doenças. Entre eles, 73 pacientes (54,9%) estavam utilizando uma categoria de MS enquanto 55 (41,3%) e 5 (3,8%) encontravam-se sob uso de duas e três categorias de MS, respectivamente. As categorias de medicações sintomáticas utilizadas em excesso variaram de analgésicos simples a triptanos e combinações de ergóticos e analgésicos com cafeína. A ingestão média por paciente por dia foi de 3 a 4 comprimidos e os compostos mais usados foram analgésicos simples (isolados ou em combinações) por 75,2% dos pacientes, drogas com cafeína por 71,4%, derivados da ergotamina por 26,1%, triptanos por 15,5%, medicamentos com narcóticos ou ansiolíticos por 13% e antinflamatórios não esteroidais por 3,8% dos pacientes. Os mecanismos pelos quais o uso excessivo de MS exerce um papel nesta transformação de padrão doloroso são incertos mas a despeito da necessidade de realização de estudos controlados para comprovar o verdadeiro papel desempenhado pelas MS no desenvolvimento da migrânea transformada, este estudo enfatiza a necessidade de se estabelecer diretrizes mais rigorosas no padrão de prescrição de sintomáticos em pacientes com cefaléias frequentes.

PALAVRAS-CHAVE: migrânea crônica (transformada), uso excessivo, medicações sintomáticas, cefaléia de rebote por analgésicos.

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The prevalence of daily headache is as high as 5% of the adult population[1]. In specialized headache centers, daily headache sufferers represent 35 to 80% of the patients that seek help[2]. Most of these patients may overuse symptomatic medications (SM) taken to relieve headache or associated symptoms[3,4]. Patients with episodic migraine may gradually develop a pattern of daily or almost daily headache, losing migraine features and presenting characteristics resembling those of the chronic tension-type headache[5,6]. The conversion to a modified pattern of migraine is known as chronic (transformed) migraine[7]. Among transformed migraine patients, over 80% have converted to the daily or near-daily pattern and maintained it as a result of the overuse of medications, therefore changing the episodic pattern into a transformed migraine one[8,9]. These patients commonly present with episodic migraine that started in the second or third decades, and around 30 to 40 years of age, the headaches become progressively more frequent with the typical migraine features of nausea, vomiting, photophobia, phonophobia and osmophobia occurring less and/or with less intensity[10,11]. Some patients start with episodic migraine with aura, which transforms into migraine without aura and daily headache occur subsequently[11,12]. Other migraine characteristics such as menstrual aggravation, identifiable migraine triggers and unilateral headache may be present[12]. Most of these patients present with a positive family history for migraine and have intermittent typical migraine attacks, of greater severity than the daily headache, known as superimposed full-blown migraine attacks[11,12].

The objective of this study was to describe the consumption profile of symptomatic medications among patients with transformed migraine attending a tertiary headache center.

METHOD

During the period from May 2000 to April 2002, 143 consecutive chronic daily headache patients with normal physical and neurological examinations, not being treated for any other medical and psychiatric illnesses and fulfilling the proposed criteria for TM and symptomatic medication (SM) overuse were studied prospectively[9,10]. All patients were attending a private subspecialty headache center, were evaluated by the first author in initial consultations not shorter than one hour and had a history of TM for longer than 6 months. In addition, the patients answered a questionnaire with details concerning the headache initiation, evolution and characteristics, as well as factors involved in its worsening, progression and their habits of symptomatic medication consumption. Because the patients included in this study had normal physical and neurological examinations and were not being treated for any other medical and psychiatric illnesses, no diagnostic studies were necessary.

The criteria used to define symptomatic medication overuse were the consumption of at least one of the following for at least one month, as proposed by Silberstein et al.[10]: 1) Simple analgesic use (>1000mg ASA/acetaminophen) >5 days / week; 2) Combination analgesics (caffeine, barbiturate-containing medications) (>3 tablets/day) >3 days / week; 3) Narcotics (>1 tablet/day) >2 days / week; 4) ergotamine use (1 mg PO or 0,5 mg PR) >2 days / week. As proposed recently, the use of triptans >3 days / week was also considered overuse of SM and the patients fulfilling such proposed criterion were also included[13].

RESULTS

Twenty-two men and 111 women, ages 17 to 80 years old (median 42.7 years) were included. One hundred twenty three patients had migraine without aura and ten patients migraine with and without aura, as primary headaches, according to the criteria of International Headache Society (IHS)[14]. The categories and brand names of overused symptomatic medications are listed in Table 1 and varied from simple analgesics such as paracetamol, aspirine and dipirone to narcotics, triptans and combinations of ergot derivatives and caffeine. Seventy-three patients (54.9%) were using one category of SM, while 55 (41.3%) and 5 (3.8%) patients were taking simultaneously two and three categories of SM respectively. Table 2 lists the distribution, among patients, of medication classes overused. Among the 133 patients, 58 (43.6%) informed that were taking the SM once prescribed by their physicians and 75 (56.4%) were self-medicating. Among the 58 patients using prescribed drugs, 21 attended a regular medical visit during the last 3 months. None of the patients were taking traditional preventive medications despite of the fact that some of them referred the intake of the overused SM to "prevent" the headache attack to become intense. The average intake per patient per day was of 3 to 4 tablets. The average intake per category used was: 1) simple analgesics: 2 to 6 tablets/day (average 3 / day); 2) NSAID: 1 to 3 tablets and/or suppositories and/or injectable ampoules/day (average 2 / day); 3) triptans: 1 to 3 tablets/day (average 2 / day); 4) ansiolitics and narcotics alone: less than 1 tablet/day; 5) combination of simple analgesics and caffeine: 2 to 8 tablets/day (average 4 / day); 6) combination of simple analgesics and narcotics: less than 1 tablet/day; 7) combination of ergot derivatives and caffeine: 1 to 3 tablets/day (average 2 / day); 8) combination of varied substances: less than 1 tablet/day.

Table 1. Categories and brand names of symptomatic medications overused.

Category	Substances	Brand names
Simple analgesics	Paracetamol (acetaminophen) salicylic acid, dipirone	tylenol, novalgina, dipirona, aspirina, paracetamol, anador, doril, bufferin
Non steroidal anti-inflammatory drugs (NSAID)	Ibuprofen, naproxen sodium, naproxen, indomethacin, sodium diclofenac, mefenamic acid, lysine clonixinate, rofecoxib, celecoxib	advil, flanax, indocid, ponstan, dolamin, vioxx, celebra, naprosyn, voltaren
Triptans	Naratriptan, rizatriptan, zolmitriptan, sumatriptan	naramig, maxalt, sumax, zomig, imigran
Ansiolitics	Bromazepan, diazepan, cloxazolam, clonazepan	lexotan, olcadil, rivotril, diempax
Narcotics	Pentazocin, codeine	dividol, codein
Combination of simple analgesics and caffeine	Dipirone + isometepthene + caffeine Dipirone + orphenadrine + caffeine Paracetamol + propiphenazone + caffeine Paracetamol + caffeine Salicylic acid + caffeine	neosaldina, dorflex, saridon, dorilax, sedalgina, excedrin, aspirina forte
Combination of simple analgesics and narcotics	Paracetamol + caffeine	tylex
Combination of ergot derivatives and caffeine	Ergotamine tartrate + caffeine + paracetamol Ergotamine tartrate + caffeine + salicylic acid + homatropine Dihidroergotamine + propiphenazone + caffeine Dihidroergotamine + paracetamol + caffeine Dihidroergotamine + dipirone + caffeine	ormigrein, tonopan, cefalium, cefaliv, migrane, parcel
Combination of varied substances	Paracetamol + phenilpropanolamine + pheniltoxolamine Dipirone + buthilescopolamine	sinutab, buscopan

DISCUSSION

Patients with frequent headaches often overuse analgesics, opioids, ergotamine derivatives and triptans[15]. In this series the majority of the patients (78.7%) were overusing more than one substance simultaneously even though it may be represented as one single category of SM. In a study of Diner and Tfelt-Hansen[16], patients averaged 2.5 to 5.8 different pharmacologic components (range 1-14). Bigal et al.[4] observed that 37.1% of 456 chronic daily headache patients were overusing two different medications, while 21.9% were taking three medications and 7% four medications, excluding caffeine. Austrian patients averaged 6.3 different headache pain drugs[17]. The number of tablets or suppositories taken daily frequently amazes physicians. While our patients averaged 3 to 4 tablets per patient per day considering the different categories of SM, the patients of Diener and Tfelt-Hansen's series[16] characterized by taking 4.9 tablets (and/or suppositories) per day (range 0.25 – 25). With regard to the pharmacological agents used, our patients overused mostly simple analgesics (isolated or in combination with other substances) (75.2%), caffeine containing drugs (71.4%), drugs containing ergotamine derivatives (26.1%), triptans (alone or combined) (15.5%), drugs with narcotics or ansiolitics (13%) and NSAID (3.7%). Differently from our series, Bigal et al.[4] demonstrated that butalbital (45.6%) and opioids (29.8%) were, along with paracetamol (43.9%), the most widely used components. In agreement with the patients of these authors, paracetamol was the most com-

Table 2. Distribution, among patients, of medication classes overused.

Categories of medication overused	Number and percentage of patients	Average intake per day (tablets or other formulations)
Simple analgesics	15 (11.3%)	2-6 (3)
Non steroidal anti-inflammatory drugs (NSAID)	3 (2.2%)	1-3 (2)
Triptans	9 (6.8%)	1-3 (2)
Ansiolitics	0	< 1
Narcotics	0	< 1
Combination of simple analgesics and caffeine	32 (24%)	2-8 (4)
Combination of simple analgesics and narcotics	3 (2.2%)	< 1
Combination of ergot derivatives and caffeine	10 (7.5%)	1-3 (2)
Combination of varied substances	1 (0.7%)	< 1
Simple analgesics + Combination of simple analgesics and caffeine	13 (9.8%)	NA
Simple analgesics + Combination of ergot derivatives and caffeine	5 (3.7%)	NA
Simple analgesics + Combination of varied substances	3 (2.2%)	NA
Non steroidal anti-inflammatory drugs (NSAID) + Combination of simple analgesics and caffeine	2 (1.5%)	NA
Non steroidal anti-inflammatory drugs (NSAID) + ansiolitics	1 (0.7%)	NA
Non steroidal anti-inflammatory drugs (NSAID) + triptans	2 (1.5%)	NA
Combination of simple analgesics and caffeine + triptans	5 (3.6%)	NA
Combination of simple analgesics and caffeine + ansiolitics	7 (5%)	NA
Combination of ergot derivatives and caffeine + Combination of simple analgesics and caffeine	11 (8.3%)	NA
Combination of ergot derivatives and caffeine + triptans	3 (2.2%)	NA
Combination of ergot derivatives and caffeine + ansiolitics	3 (2,2%)	NA
Simple analgesics + Combination of simple analgesics and caffeine + triptans	1 (0.7%)	NA
Simple analgesics + Combination of ergot derivatives and caffeine + ansiolitics	3 (2.2%)	NA
Combination of simple analgesics and caffeine + triptans + narcotics	1 (0.7%)	NA

NA, not applicable.

monly used substance by the patients of Schneider et al.[17] and Silberstein and Saper (34.9%).[18]. On the other hand, in a series of 225 patients with chronic daily headache evaluated by Krymchantowski et al.[19] the authors also noted that caffeine compounds were the mostly overused medication (87.4%), followed by dipirone (68.3%), ergotamine derivatives (48.2%) and paracetamol (42.2%).

Almost all acute care medications for headache, including over-the-counter analgesics, tranquilizers, barbiturates, opioids, ergotamine compounds and triptans can be associated with the development of transformed migraine and chronic daily headache[4]. The mechanisms by which the overuse of symptomatic medications (SM) play a role in this transformation are uncertain. Srikiatkhachorn & Anthony[20] emphasized that patients with drug induced daily headache present a higher concentration of 5-HT2 receptors in platelet membranes compared to episodic migraine patients, suggesting that this could be found in central serotonergic receptors as well and explain the transformation of episodic migraine into daily headache associated with overuse of drugs. Bowdler et al.[21] and Lance et al.[22] suggested that patients with

primary headaches specially migraine, develop a pattern of daily headache in the presence of various kinds of symptomatic medications (SM) overuse. These authors pointed to the fact that a higher suppression, induced by the SM, over an already deficient antinociceptive system may play a role in this pattern of transformation. Srikiatkhachorn et al.[23] suggested that the excessive use of SM could lead to an up-regulation of central serotonergic receptors suppressing therefore the function of serotonergic pathways involved in central pain modulation. Hering et al.[24] observed an increase in blood level of serotonin after withdrawal of overused SM in chronic daily headache patients. In addition, these authors analyzed the platelet membrane transduction of patients with daily headache suggesting that the overuse of SM would result in a modification of this process, possibly playing a role in such a headache pattern modification[25].

Despite all of those proposed mechanisms, analgesic rebound headache has not been yet demonstrated in placebo-controlled studies with the exception of caffeine. In a controlled study of caffeine withdrawal, 64 normal adults (71% women) with low to moderate caffeine intake (the equivalent of about 2.5 cups of coffee/day) were given a 2-day caffeine-free diet and either placebo or replacement caffeine. Under double-blind conditions, 50% of the patients who were given placebo had a headache by day 2 compared to 6% of those given caffeine. In addition, withdrawal symptoms such as nausea, depression and flu-like symptoms were common in the placebo but not in the caffeine group. This study is a relevant short-term model for caffeine withdrawal since caffeine-containing medications are commonly overused by chronic (transformed) migraine patients, and were the mostly overused component of our group of patients. Specific limits are also necessary to prevent analgesic, ergotamine and triptan overuse. Since rebound may develop in patients taking as little as 0.5 to 1 mg of ergotamine three times a week[26], the use of this substance have to be limited to a maximum of 2 times a week. With regard to triptans, three times a week is the limit recommended by Silberstein and Lipton[13]. The present study corroborates the high prevalence of overusing symptomatic medications by transformed migraine patients seen in specialized centers. Even though controlled trials are essential to demonstrate the real role of such compounds in the development of transformed migraine and chronic daily headache, it emphasizes the necessity for more rigorous prescribing guidelines for patients with frequent headaches.

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