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Medication-overuse headache: citalopram associated with analgesics withdrawal as possible treatment

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Abstract Medication-overuse headaches are a relevant medical and social problem, for which specific treatments have not yet been defined. In patients with chronic daily headache who take analgesics every day, this headache is most likely to be caused by drugs and will vanish with abstinence. Nonetheless, there is anecdotal evidence that selective serotonin reuptake inhibitors (SSRI) are effective in chronic daily headache, because of the concomitant presence of psychiatric comorbidities (depression, anxiety, or a combination of both). Six migraineurs were admitted to the Neurology Clinic for medication-overuse headache and associated depression, anxiety and behavioural changes. Treatment consisted in suppressing other drugs and by using an SSRI, citalopram, at modest dosage (≤30 mg daily). Analgesic withdrawal was performed in hospital and was not particularly problematic. Over a 1-year follow-up, pain coping strategies ameliorated and depression decreased; drug withdrawal was easy, even from barbiturates, and pain control was good. Further investigation into the possible use of citalopram or other SSRIs in medication-overuse headache is waranted.

Key words Medication abuse • Overuse • Headache • Depression • Serotonin • SSRI • Citalopram

Introduction

Chronic daily headache is a specific entity, characterized by almost daily headache. The term, which does not exist in the present classification of the International Headache Society (IHS) [1], is widely used by different specialists in different meanings. Actually, the term comprises all the patients with daily or nearly daily headache and headache duration of four hours or more and includes, in decreasing frequency of occurrence: chronic tension-type headache, medication-overuse headache, transformed migraine, hemicrania continua and new daily persistent headache [2]. Probably, chronic tension-type headache leads to medication overuse headache, which may be considered intimately related and probably is a unique situation, where one condition is the inevitable conclusion of the other.

Chronic tension-type headache is a diffuse, dull, non-localized headache without or with minimal autonomic features. Headache intensity is lower than that of migraine, and most often is described as a feeling of increased pressure around the head. The definition of IHS [1] requires that daily headache is present for more than six months. The exact pathogenesis of tension-type headache is unknown, and many different causes have been evoked: decreased central pain threshold, inadequate processing of inputs deriving from muscle contraction, altered relationship between soft tissue and joints [3, 4].

Very often, this pain requires a constant intake of drugs. Inappropriate use of headache medication for the treatment

of headache episodes may contribute to the maintenance of pain and loss of response to most treatments.

As Diener [4] reported, almost no experimental work has been done in this field, and although many treatments have been described, evidence is anecdotal. If a patient complains of chronic daily headache and takes pain medication every day, this headache is most likely to be caused by drugs and will vanish with abstinence [4]. Thus, the most difficult part of the question lies in the intimate knowledge and awareness of the patient regarding his abuse. Most often depressed mood, anxiety and altered response to stress cause (or enforce) pain resistance. All considered, stopping all medications is a well-recognized and successful therapy for medication-overuse headache [5].

We present six patients with typical medication-overuse headache, who were treated by abstinence of analgesics and concomitantly by a specific antidepressive drug.

Case series

Six patients with medication-overuse headache came to our observation between August 1999 and August 2001 (Table 1). Neurological and laboratory examinations were normal in all patients. Chest radiography, electrocardiography (ECG) and computed tomography (CT) of the head were also normal. Mood was tested on Zung's autoevaluation for depression [5] (SDS score) and with the Hamilton test [6]. Pain intensity and illness experience were scored on the illness behaviour inventory (IBI) test [7] and on the present pain intensity (PPI) scale of the short form of the McGill pain assessment questionnaire (SF-MPQ) [8].

After obtaining written informed consent, we interrupted the administration of all analgesics drugs the patients had previously assumed, and began oral administration of citalopram HBr, beginning with 10 mg daily, then gradually increasing to 30 mg daily over 10 days. Patients were instructed to take naproxen (500 mg) for relief of headache symptoms only when migraine occurred. During the first 2–3 days, two patients developed nausea. Since the general examination was normal, we attributed this symptom to drug withdrawal and treated it with metoclopramide intramuscularly when necessary. After the fourth day, this treatment was no longer necessary.

Gradually, the pain relief ameliorated the patients' quality of life, which was reflected by their increased compliance. After three months, patients reported a remission of con-

Table 1 Baseline characteristics of 6 patients with medication-overuse headache

Case	Diagnosis	Headache period prior to treatment	Medication overused	Zung score	Hamilton score	IBI score	SF-MPQ score
1	Catamenial migraine without aura	8 months	Rizatriptan RPD Acetylsalicylic acid plus metoclopramide (up to 3600 mg/daily) Butalbital (200–300 mg/daily) Other NSAIDs	59.2%	42	62	4
2	Migraine with visual aura	10 months	Acetylsalicylic acid plus metoclopramide (up to 1800 mg/daily) Butalbital (150–200 mg/daily) Barbiturates plus paracetamole and codeine (codeine, 60–90 mg/daily)	62.3%	43	56	4
3	Catamenial migraine without aura	7 months	Rizatriptan RPD (up to 20 mg/daily) Acetylsalicylic acid plus metoclopramide (up to 2400 mg/daily) Butalbital (200–300 mg/daily)	61.2%	42	67	3
4	Migraine without aura	8 months	Zolmitriptan (up to 5 mg twice daily or three times per week) Acetylsalicylic acid (up to 2400 mg/daily) Butalbital (200–300 mg/daily) Other NSAIDs	59%	39	68	4
5	Migraine without aura	12 months	Rizatriptan RPD (up to 20 mg/daily, three or four times per week) Acetylsalicylic acid plus metoclopramide (up to 3600 mg/daily) Butalbital (200–300 mg/daily)	47%	27	54	3
6	Migraine with visual aura	6 months	Acetylsalicylic acid (up to 2000 mg/daily) Butalbital (200–300 mg/daily) Barbiturates plus paracetamole and codeine (codeine, 60–90 mg/daily)	42.3%	32	46	4

NSAIDs, non-steroidal anti-inflammatory drugs

Table 2 Test scores of the 6 patients after one year of treatment

Case	Zung score	Hamilton score	IBI score	SF-MPQ score
1	19.2%	11	22	1
2	15%	21	20	1
3	22%	9	21	1
4	10%	9	22	1
5	13%	12	15	1
6	10%	12	10	1

strictive pain and even a diminishment in the intensity of pain during migraine attacks. At this time, citalopram was reduced to 20 mg daily. The patients reported an improvement of mood (Table 2). During the 1-year follow-up, the patients never reported constrictive headache and migraine attacks were of minor intensity.

Discussion

Inappropriate use of medication for the treatment of headache episodes may contribute to the development of chronic headache, which can become refractory to most drugs. Prevalence and incidence rates of chronic medication-overuse headache are rarely reported; most headache centres report that 5%–10% of all patients treated have medication-overuse headache [10]. Medication-overuse headache is a major health problem [10]. Patients with migraine and tension-type headache have a higher potential for medication-overuse headache [11], and relapses of migraine occur in migraineurs who have been placed on analgesics for other ailments. On the contrary, chronic overuse of analgesics does not cause increased headache in non-migraineurs [12, 13].

Patients with analgesic-overuse headache have a different psychologic substrate than psychiatric substance abusers, although psychiatric assessment and support may be beneficial for them [14]. In a long-term follow-up (2–4 years after withdrawal of therapy), 48.5% of patients suffered an abuse relapse within 4 years and developed drug-induced headache again [15]. What clearly emerged is that a successful long-term approach is connected with a significant reduction of the frequency of headache attacks. Only under relapse conditions, the patients reached their former headache frequency level [15].

Treatment recommendations include fluid replacement, analgesics, tranquilizers, neuroleptics, and amitriptyline, [4, 16], but usually the most important point is drug withdrawal, not always easy, especially in cases involving abuse of barbiturates, opiate or codeine. One means of drug withdrawal, as suggested by Hering and Steiner [17], is to abruptly withdraw the offending drugs, offer adequate explanation of the disorder, regular follow-up, and use amitriptyline (10 mg at night) and naproxen (500 mg) for relief of headache symptoms.

Patients with analgesic overuse headache, as well as those with chronic combination headache, exhibit more psychopathology than controls [18]. One study of both migraine and tension headache found a relationship between depression and pain, and improvement only for those with tension headache, curing depression [19]. Meta-analysis of 38 randomized controlled trials suggested that antidepressants are effective in reducing chronic headache pain [20]. Patients receiving antidepressants were twice as likely to improve, and had a mean reduction in headache burden of nearly 1 standard deviation and a reduced analgesic consumption corresponding to 0.7 standard deviations [20]. Analgesic properties of SSRI are known but not well understood [21]. Pain and depression are tightly bound [22].

Considering that a successful long-term therapy for medication-overuse headache is connected with a significant reduction of the frequency of headache attacks, that there is a relapse of drug misuse in 48.5% of cases within 4 years from treatment [15] and that patients who abused caffeine combined with analgesics or barbiturates showed a higher relapse risk, we decided to employ specific SSRI therapy in our department. All patients were treated with citalopram and showed encouraging results. The number of treated patients is not high, but one year of follow-up has been obtained. Analgesic withdrawal was performed in hospital, which may explain why it was not particularly problematic. Pain coping strategies ameliorated as depression decreased; we obtained an easy withdrawal, even from barbiturates and other analgesics, an amelioration of mood and an amelioration coping (as showed by IBI and PPI scores), and good pain control lasting for one year of follow-up.

We chose citalopram due to the general lack of side effects, good tolerance and excellent results in depression. It has been used previously in medication-overuse headache treatment [23], without encouraging results.

The mechanism of action of citalopram HBr as an antidepressive is presumed to be linked to potentiation of serotoninergic activity in the central nervous system (CNS), resulting from its inhibition of CNS neuronal reuptake of

serotonin, with minimal effects on norepinephrine and dopamine neuronal uptake. Tolerance to the inhibition of serotonin uptake is not induced by long-term treatment.

Therapy can be protracted, without side effects (especially anxiety, nausea or vomiting, often reported with other SSRI). We obtained good results in all patients, by using small doses of drugs.

In our work, we examined the effects of citalopram associated with analgesic suppression in the treatment of medication-overuse headache. It is not yet known if the positive outcome is due to the antidepressant properties of citalopram or to the withdrawal of analgesics.

In medication-overuse headache, where nothing has been definitely written, citalopram may be suggested as an adjunctive therapy. However, the most important preventive measure remains proper instruction and an appropriate surveillance of patients, who should be instructed to use specific antimigraine drugs only for migraine attacks.

References

1. – (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society Cephalalgia 8[Suppl 7]:1–93
2. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near daily headaches: field trial of revised IHS criteria. Neurology 47(4):871–875
3. Olesen J, Diener HC (1996) Tension type and cervicogenic headache. In: Brandt T, Caplan LR, Dichgans J, Diener HC, Kennard C (eds) Neurological disorders: course and treatment. Academic, San Diego, pp 29–36
4. Diener HC (2001) Chronic daily headache. American Academy of Neurology, Philadelphia, 7AS.004–9–18
5. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V (2001) Clinical features of withdrawal headache following overuse of triptans and other headache drugs. Neurology 57(9):1694–1698
6. Zung WWK (1965) A self-rating depression scale. Arch Gen Psychiatry 12:63–70
7. Hamilton M (1967) Development of a rating scale for primary depressive illness. Br J Clin Psychol 6:278–296
8. Turkat ID, Pettegrew LS (1983) Development and validation of the illness behaviour inventory. J Behav Assess 5:35–41
9. Melzak R (1987) The short-from McGill pain questionnaire. Pain 30:191–197
10. Castillo J, Munoz P, Guitera V, Pascual J (1999) Epidemiology of chronic daily headache in the general population. Headache 39:190–196
11. Bahra A, Walsh M, Menon S, Goadsby PJ (2000) Does chronic daily headache arise de novo in association with regular analgesic use? Cephalalgia 20:294 (abstract)
12. Lance F, Parkes C, Wilkinson M (1988) Does analgesic abuse cause headache de novo? Headache 38:61–62
13. Diener HC, Dahlof CGH (1999) Headache associated with chronic use of substances. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches, 2nd edn. Lippincott Williams Wilkins, Philadelphia, pp 871–878
14. Young WB (2001) Medication overuse headache. Curr Treat Options Neurol 3(2):181–188
15. Fritsche G, Eberl A, Katsarava Z, Limmroth V, Diener HC (2001) Drug-induced headache: long-term follow-up of withdrawal therapy and persistence of drug misuse. Eur Neurol 45(4):229–235
16. Dodick DW (2001) Chronic daily headaches of long-duration. American Academy of Neurology, Philadelphia, 7PC.001–70–77
17. Hering R, Steiner TJ (1991) Abrupt outpatient withdrawal of medication in analgesic abusing migraineurs. Lancet 337:1442–1443
18. Ham LP, Andrask F, Packard RC, Bundrick CM (1994) Psychopathology in individuals with post-traumatic headaches and other pain types. Cephalalgia 14(2):118–126
19. Denaro A, Martucci N, Ruggieri S, Manna V, Agnoli A (1985) Headache and noradrenergic involvement: the effects of alpha-2 stimulants and alpha 1 antagonists. Acta Psychiatr Scand 72(S320):20–25
20. Tomkins GE, Jackson JL, O'Malley PG, Balde E, Santoro JE (2001) Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med 111:54–63
21. Sawynok J, Esser MJ, Reid AR (2001) Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. J Psychiatry Neurosci 26(1):21–29
22. Corruble E, Guelfi JD (2000) Pain complaints in depressed inpatients. Psychopathology 33:307–309
23. Bendetsen L, Jensen R, Olesen J (1996) A non selective (amitriptyline) but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension type headache. J Neurol Neurosurg Psychiatry 61(3):285–290