Eur J Med Res (2004) 9: 565-569

CLINICAL FEATURES AND THERAPY OF MEDICATION OVERUSE HEADACHE

I. Kavuk[1,2], Z. Katsarava[1], M. Selekler[3], K. Sayar[4],M. W. Agelink[2], V. Limmroth[1], H. C. Diener[1]

[1]Department of Neurology, University of Diusburg-Essen, Germany
[2]Department of Biological Psychiatry and Neuroscience, Ruhr-University of Bochum, Germany
[3]Department of Neurology, University of Kocaeli, Turkey
[4]Bakirkoy State Hospital for Research and Training in Neurology and Psychiatry, Istanbul, Turkey

Abstract: Inappropriate use of headache medication (>15 times/month) for the treatment of headache episodes may contribute to the development of chronic headache which is refractory to most treatments. Physicians experienced in the treatment of migraine and other headaches are well aware that the daily intake of antipyretic or antiinflammatory analgesics, opioids, ergot alkaloids and "triptans" may result in chronic daily headache. Conversely, if a patient complains of chronic headache and takes pain medication every day, this headache is most likely to be caused and sustained by the medication and will vanish or improve with abstinence. Treatment includes drug withdrawal followed by structured acute therapy and initiation of migraine prophylactic treatment.

Key words: Medication overuse headache; Epidemiology; Clinical features; Therapy

INTRODUCTION

The frequent use (>15 times/month) of medication for the treatment of acute migraine attacks may cause medication overuse headache [1]. This kind of headache can be caused by the intake of combination analgesics, opioids, ergot alkaloids and triptans [2]. The time between first intake and daily headache is shortest for triptans (1-2 years), longer for ergots (3-5 years) and longest for analgesics (5-10 years). Treatment includes drug withdrawal followed by structured acute therapy and initiation of migraine prophylactic treatment.

Since 2003 the classification of the International Headache Society (IHS) from 1988 was used [47], but it had lacked precision about triptan induced headaches. Some authors studied the clinical features of triptan misuse and described typical signs of this syndrome [28, 43, 48-50]. Based on this information the IHS created new classification criteria for drug induced headache in 2003 [51].

Up to now no experimental work has been done in this field, and the following review is based mainly on clinical series describing patients presenting at headache clinics with this problem, with subsequent treatment and follow-up.

PREVALENCE

Prevalence rates of chronic medication overuse headache are rare [3]. Our own data revealed that approx. 3.6 % suffer from chronic daily headache [4]. To produce these figures, 523 employees of a large textile manufacturer were asked about headaches within the preceding 12 months according to criteria of the International Headache Society. Probands with headaches were studied by a neurologist. As a comparator group, Turkish migrants also employed there were also consulted. Amongst such individuals, the proportion of chronic daily headache patients was significantly higher at 10.7%. In a Spanish population based study, about 1% of the population suffered from daily headache combined with medication-overuse headache [5]. Most headache centers report that between 5% and 10% of the patients they see fulfil the criteria of medication overuse headache [6]. Micieli et al. observed an incidence of 4.3% in 3,000 consecutive headache patients [7]. Patients with cluster headache almost never develop medication overuse headache. A survey in family doctors showed, that medication overuse headache was the third most common cause of headache [8]. Taken together, these studies indicate that medication overuse headache is a major health problem. This is also true if one considers the side effects of chronic intake of analgesics, ergotamine and triptans.

Most headache experts agree that patients with migraine and tension-type headache have a higher potential for medication overuse headache [9]. Relapses of migraine occur in migraineurs who have been placed on analgesics for other ailments. The association between analgesic overuse and headache has been studied in conditions other than primary headache disorders. Chronic overuse of analgesics does not cause increased headache in nonmigraineurs [9]. For example, a group of arthritis patients who were consuming fairly large amounts of analgesics regularly for arthritis did not show increased incidence of headache [10]. The conclusion drawn from various clinical observations and studies is that medication overuse headache may be restricted to those who are already headache sufferers. The basis for this could either be genetic or the fact that migraine pain is more severe than joint pain. Different mechanisms probably contribute to the transition from the original headache to medication overuse headache. Psychological factors include the reinforcing properties of pain relief by drug consumption, a very powerful component of positive conditioning. Many patients report taking migraine drugs prophylactically because they are worrying about missing work (or, inevitably, the job) or missing an impor-

tant social event (dinner, theatre, etc.). More importantly, patients often fear an imminent headache and take analgesics or specific migraine drugs prophylactically. They are often instructed by the physicians or by the instructions supplied with the medication to take the migraine drug as early as possible at the start of either the aura or the headache phase of a migraine attack.

Withdrawal headache is an additional factor. Whenever the patient tries to stop or reduce the medication, a worsening of the pre-existing headache occurs. Barbiturates are contained in drugs for the treatment of tension-type headache and have a high potency for addiction and cause headache. The psychotropic side effects of analgesic or migraine drugs such as sedation or mild euphoria and their stimulating action may lead to drug dependency. Barbiturates, codeine, other opioids and caffeine are the most likely substances to have this effect. Caffeine increases vigilance, relieves fatigue, and improves performance and mood. The typical symptoms of caffeine withdrawal such as irritability, nervousness, restlessness, and especially "caffeine withdrawal headache" [11, 12], which may last for several days, encourage the patients to continue their abuse. Despite the fact that caffeine may enhance the analgesic action of acetylsalicylic acid and acetaminophen, it should be removed from analgesics. Similarly, caffeine and meprobamat, the main metabolite of carisoprodol, should be removed from ergotamine containing formulations.

There are reports on physical dependence on codeine and other opioids in headache patients [13, 14]. There are no studies that have investigated the effects of codeine intake over periods as long as 10 years as many headache patients have done. It should be remembered that up to 10% of codeine is metabolized to morphine.

Ergotamine and DHE may certainly lead to physical dependency [15]. Many patients who feel a migraine attack may take ergotamine as prophylactic treatment. The reason for the physical dependency on ergotamine remains obscure. In one study the tyramine-induced mydriasis after ergotamine administration was increased during abuse but not after withdrawal of ergotamine, indicating a central inhibition of pupillary sympathetic activity during abuse [16]. Thus a possible CNS effect of ergotamine can be observed after chronic use but not after a single dose of the drug. Other studies investigating the effect of chronic use of ergotamine on the CNS regulation of the autonomic nervous system are needed.

Clinical Symptoms

For the purpose of this publication, a meta-analysis was performed summarizing 29 studies comprising a total of 2,612 patients with chronic medication overuse headache (for details see [17]. Sixty-five percent of the patients reported migraine as primary headache, 27% of patients reported tension-type headache, and 8% of patients reported mixed or other headaches (e.g., cluster headache). Women were more prone to medication overuse headache than men (3.5:1; 1,533 women, 442 men). This ratio is slightly higher than could be expected from the gender differences in frequency of migraine. The mean duration of primary headache was 20.4 years . The mean admitted time of frequent drug intake was 10.3 years and the mean duration of daily headache was 5.9 years.

The drugs leading to chronic medication overuse headache vary considerably in the different series depending probably on both selection of patients, (e.g., "pure" ergotamine abusers being reported), and cultural factors. Probably potentially each component contained in analgesics or drugs for the treatment of migraine attacks can induce headache. This is also true for acetylsalicylic acid and paracetamol [14]. It is, however, difficult to identify a single substance as 90% of patients take more than one compound at a time. Four studies [7, 19-21] investigated the frequency of the chemical compounds of drugs used. Combination analgesics containing butalbital (short acting barbiturate), caffeine, aspirin with or without codeine were the leading candidates for medication overuse headache in one study [21]. Sumatriptan can also lead to medication overuse headache. This was first observed in patients who abused ergotamine [22, 23]. Later de novo cases were reported [24-26]. Recently patients who developed drug induced headache from naratriptan and zolmitriptan were reported [27, 28]. Due to the delay between frequent intake of triptans and the development of medication overuse headache, it is likely, that similar cases will be observed in future with the other recently approved triptans (rizatriptan, eletriptan, frovatriptan, almotriptan). The risk appears to be particularly high in headache patients with a former history of misuse of analgesics and/or ergotamine. Results from headache diaries show that the number of tablets or suppositories taken per day averages 4.9 (range 0.25-25). Patients take on average 2.5-5.8 different pharmacological components simultaneously (range 1-14).

Our most recent prospective study shows the characteristics of medication overuse headache [27]. In a prospective study 96 patients which suffered on headache at least on 10 days per month and which took any kind of symptomatic medication at least on 10 days per month underwent withdrawal from their medication. The medication overuse headache was only diagnosed in patients with significant improvement of their headache situation following withdrawal therapy one month later. As in most previous studies the majority of our patients was female (f:m ratio 4:1). Seventy-one percent of the patients reported migraine as primary headache, 14% of patients reported tension-type headache and 15% of patients reported combination headache (migraine and tension-type headache). The mean duration of primary headache was 22 years. The mean duration of drug overuse was 6,5 years. Forty-eight percent of the patients took analgesics, 40% triptans, and only 12% of patients overused ergot alkaloids. This was a clear difference to previous studies. The overuse of triptans - at least in this study - outnumbered ergotamine misuse by far. This might reflect the fact that despite high costs triptans became widely used (and overused) and suggests that triptan lately became the most important

group to cause medication overuse headache. Unlike patients suffering from medication overuse headache following intake of ergots or analgesics, patients with triptan-induced headache did not describe the typical tension-type headache but rather a migraine-like daily headache or a significant increase in migraine frequency. Furthermore the delay between frequent intake of medication and development of daily headache was shortest for triptans (1,7 years), longer for ergots (2,7 years) and longest for analgesics (4,8 years). Similarly the amount of intake of single dosages per month was lowest for triptans (18 single dosages per month), higher for ergots (37 single dosages per month) and highest for analgesics (114 single dosages per month).

The withdrawal headache experienced after stopping of medication resembles a severe and prolonged migraine attack in patients with migraine as primary headache.

Recognizing Medication Overuse Headache

Several clinical characteristics are helpful in identifying the occurrence of analgesic rebound headache in patients with primary headache disorders [21]. The following are the clinical features of medication overuse headache:

- The headaches are refractory, daily, or nearly daily.
- The headaches occur in a patient with primary headache disorders who use immediate relief medications very frequently, often in excessive quantities.
- The headache itself varies in its severity, type, and location from time to time.
- The slightest physical or intellectual effort may bring on headache. In other words, the threshold for head pain appears to be low.
- Headaches are accompanied by asthenia, nausea and other gastrointestinal symptoms, restlessness, anxiety, irritability, memory problems, and difficulty in intellectual concentration and depression. Those consuming large quantities of ergot derivatives or triptans may exhibit cold extremities, tachycardia, paresthesias, diminished pulse, hypertension, lightheadedness, muscle pain of the extremities, weakness of the legs, and depression.
- There is evidence of tolerance to analgesics over time, with patients needing progressively larger doses.
- Withdrawal symptoms are observed when patients are taken off pain medications abruptly.
- Spontaneous improvement of headache occurs on discontinuing the medications.
- Concomitant prophylactic medications are relatively ineffective while the patients are consuming excess amounts of immediate relief medications.

Prognosis

The success rate of withdrawal therapy within a time window of 1--6 months is 72.4% (17 studies, N = 1,101 patients). Success is defined as no headache at all or an improvement of more than 50% in terms of headache days. Three studies had a longer observation period between 9 and 35 months [19, 29, 30]. The success rates in these studies were 60, 70, and 73%, respectively. A 5-year follow up study found a relapse rate of 40% [29].

Management

Abrupt drug withdrawal is the treatment of choice for medication overuse headache. There are, however, no prospective and randomized trials comparing continuation of drug intake and drug withdrawal. A survey of 22 studies dealing with therapy of drug-induced headache shows that most centers used drug withdrawal as the primary therapy. (see [17]). Clinical experience indicates that medical and behavioral headache treatment fails, as long as the patient continues to take symptomatic drugs daily. The typical withdrawal symptoms last for 2--10 days (average 3.5 days) and include withdrawal headache, nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness. Seizures or hallucinations were only rarely observed even in patients abusing barbiturate-containing migraine drugs.

Drug withdrawal is performed differently. Most authors prefer inpatient programs. Hering and Steiner [31] abruptly withdrew the offending drugs on an outpatient basis by adequate explanation of the disorder, regular follow-up, and amitriptyline (10 mg at night) and naproxen (500 mg) for relief of headache symptoms. A consensus paper by the German Migraine Society [32] recommends outpatient withdrawal for patients who do not take barbiturates or tranquilizers with their analgesics and are highly motivated. Inpatient treatment should be performed in patients who take tranquilizers, codeine, or barbiturates who failed to withdraw the drugs as outpatients or who have a high depression score.

Treatment recommendations for the acute phase of drug withdrawal vary considerably between the 22 studies mentioned above. They include fluid replacement, analgesics, tranquilizers, neuroleptics, amitriptyline, valproate, intravenous DHE, oxygen, and electrical stimulation. Valproate has been shown to have beneficial effects in the prophylactic treatment of chronic daily headache complicated by excessive analgesic intake [33]. A recent large open trial showed, that cortisone effectively reduces withdrawal symptoms including rebound headache [34]. A double-blind study showed a single subcutaneous dose of sumatriptan to be better than placebo in the treatment of ergotamine withdrawal headache but the headache reappeared within 12 hr [35]. An open randomized study indicated that naproxen was better than symptomatic treatment with antiemetics and analgesics [36]. Further double-blind controlled trials are needed.

If more than three migraine attacks per month continue after withdrawal, medical and behavioral prophylaxis should be initiated. The clinical experience shows that many patients respond to prophylactic treatment, e.g., with beta- blockers or flunarizine, after drug withdrawal despite the fact that these drugs

seemingly had been unsuccessful before. Ergotamine, triptans and possibly analgesics counteract the action of prophylactic therapy and will not improve drug-induced headache. The same phenomenon can be observed for the action of amitriptyline and behavioral therapy in patients with tension-type headache.

Prevention

The most important preventive measure is proper instruction and an appropriate surveillance of patients. The migraine patients at risk often have a mixture of migraine and tension-type headaches and should be instructed carefully to use specific antimigraine drugs only for migraine attacks. This point was already stressed in 1951 by Peters and Horton concerning ergotamine abuse, i.e., complications can be avoided if enough time is taken for proper instruction of the patient, so that he or she can distinguish between vasodilating and nondilating headache [37].

Restricting the dose of ergotamine per attack (4 mg ergotamine), per week (no more than twice per week) and per month (no more than 20 mg ergotamine) is also helpful in avoiding dependency [38-41]. In a similar way, the number of doses of triptans should be limited per attack and to 12 doses per month [42, 43]. Migraine drugs that contain barbiturates, codeine, or tranquilizers as well as mixed analgesics should be avoided [44, 45]. Probably an early start of migraine prophylaxis, either by medical or behavioral treatment, can be a preventive measure to avoid drug-induced headache [46, 52].

References

1. Kavuk I, Katsarava Z, Diener HC. Epidemiology of headache. In: Diener HC (ed) The headaches. 1st ed. Stuttgart: Thieme, 2003: pp. 10-16.
2. Kavuk I, Yavuz A, Cetindere Ü, Agelink MW, Diener HC. Epidemiology of Chronic Daily Headache. Eur J Med Res 2003;8:236-240.
3. Kavuk I, Katsarava Z, Stang A, Agelink MW, Diener HC. New recent information about the epidemiology of headache. Fortschr Neurol Psych 2003;71:1-8.
4. Kavuk I, One-Year Prevalence of Chronic Daily Headache in Turkish Immigrants and German Natives. J Neurol 2003;1:I/146-147.
5. Castillo J, Munoz P, Guitera V, Pascual J. Epidemiology of chronic daily headache in the general population. Headache 1999;39:190-196.
6. Granella F, Farina S, Malferrari G, Manzoni GC. Drug abuse in chronic headache: a clinico-epidemiologic study. Cephalalgia 1987;7:15-19.
7. Micieli G, Manzoni GC, Granella F, Martignoni E, Malferrari G, Nappi G. Clinical and epidemiological observations on drug abuse in headache patients. In: Diener HC, Wilkinson M (eds) Drug-Induced Headache. Berlin Heidelberg New York, Springer 1988: pp. 20-28.
8. Rapoport A, Stang P, Gutterman DL, Cady R, Markley H, Weeks R, et al. Analgesic rebound headache in clinical practice: data from a physician survey. Headache 1996; 36:14-19.
9. Bahra A, Walsh M, Menon S, Goadsby PJ. Does chronic daily headache arise de novo in association with regular analgesic use? Cephalalgia 2000;20:294 [abstract].
10. Lance F, Parkes C, Wilkinson M. Does analgesic abuse cause headache de novo? Headache 1988;38:61-62.
11. Silverman K, Evans SM, Strain EC, Griffiths RR. Withdrawal syndrome after the double-blind cessation of caffeine consumption. New Engl J Med 1992;327:1109-1114.
12. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. Br Med J 1990;300:1558-1559.
13. Fisher MA, Glass S. Butorphanol (Stadol): A study in problems of current drug information and control. Neurology 1997;48:1156-1160.
14. Ziegler DK. Opiate und opioid use in patients with refractory headache. Cephalalgia 1994;14:5-10.
15. Saper JR, Jones JM. Ergotamine tartrate dependency: features and possible mechanisms. Clin Neuropharmacol 1986;9:244-256.
16. Fanciullacci M, Alessandri M, Pietrini U, Briccolani-Bandini E, Beatrice S. Long-term ergotamine abuse: effect on adrenergically induced mydriasis. Clin Pharm Ther 1992; 51:302-307.
17. Diener HC, Dahlöf CGH. Headache associated with chronic use of substances. In: Olesen, J., Tfelt-Hansen, P., Welch, K. M. A. (eds) The Headaches, 2nd edition, Lippincott, Williams & Wilkins, Philadelphia 1999: pp. 871-878.
18. Rapoport A, Weeks R, Sheftell F. Analgesic rebound headache: theoretical and practical implications. In: Olesen J, Tfelt-Hansen P, Jensen K (eds) Proceedings Second International Headache Congress, Copenhagen. Copenhagen; 1985: pp. 448-449.
19. Baumgartner C, Wessely P, Bingöl C, Maly J, Holzner F. Longterm prognosis of analgesic withdrawal in patients with drug-induced headaches. Headache 1989;29:510-514.
20. Diener HC, Bühler K, Dichgans J, Geiselhart S, Gerber WD, Scholz E. Analgetikainduzierter Dauerkopfschmerz. Existiert eine kritische Dosis? Arzneimitteltherapie 1988; 6:156-164.
21. Mathew NT, Kurman R, Perez F. Drug induced refractory headache - clinical features and management. Headache 1990;30:634-638.
22. Catarci T, Fiacco F, Argentino C, Sette G, Cerbo R. Ergotamine-induced headache can be sustained by sumatriptan daily intake. Cephalalgia 1994;14:374-375.
23. Kaube H, May A, Diener HC, Pfaffenrath V. Sumatriptan misuse in daily chronic headache. BMJ 1994;308:1573.
24. Gaist D, Hallas J, Sindrup SH, Gram LF. Is overuse of sumatriptan a problem? A population-based study. Eur J Clin Pharmacol 1996;3:161-165.
25. Gaist D, Tsiropoulus I, Sindrup SH, Hallas J, Rasmussen BK, Kragstrup J. Inappropriate use of sumatriptan: population based register and interview study. Brit J Med 1998; 316:1352-1353.
26. Pini LA, Trenti T. Case report: does chronic use of sumatriptan induce dependence? Headache 1994;34:600-601.
27. Katsarava Z, Fritsche G, Diener HC, Limmroth V. Drug-induced headache (DIH) following the use of different triptans. Cephalalgia 2000;20:293 [abstract].
28. Limmroth V, Kazarawa S, Fritsche G, Diener HC. Headache after frequent use of new 5-HT agonists zolmitriptan and naratriptan. Lancet 1999;353:378.
29. Schnider P, Aull S, Baumgartner C, Merterer A, Wöber C, Zeiler K, et al. Long-term outcome of patients with headache and drug abuse after inpatient withdrawal: five year follow-up. Cephalalgia 1996;16:481-485.
30. Diener HC, Dichgans J, Scholz E, Geiselhart S, Gerber WD, Bille A. Analgesic-induced chronic headache: long-term results of withdrawal therapy. J Neurol 1989;236:9-14.
31. Hering R, Steiner TJ. Abrupt outpatient withdrawal of medication in analgesic-abusing migraineurs. Lancet 1991; 337:1442-1443.

32. Haag G, Baar H, Grotemeyer KH, Pfaffenrath V, Ribbat MJ, Diener HC. Prophylaxe und Therapie des medikamenteninduzierten Dauerkopfschmerzes. Schmerz 1999; 13:52-57.
33. Mathew NT, Ali S. Valproate in the treatment of persistent chronic daily headache. An open labeled study. Headache 1991;31:71-74.
34. Krymchantowski AV, Barbosa JS. Prednisone as initial treatment of analgesic-induced daily headache. Cephalalgia 2000;20:107-113.
35. Diener HC, Haab J, Peters C, Ried S, Dichgans J, Pilgrim A. Subcutaneous sumatriptan in the treatment of headache during withdrawal from drug-induced headache. Headache 1990;31:205-209.
36. Mathew NT. Amelioration of ergotamine withdrawal with naproxen. Headache 1987;27:130-133.
37. Peters GA, Horton BT. Headache: with special reference to the excessive use of ergotamine preparations and withdrawal effects. Proceed Staff Meet Mayo Clin 1951;26: 153-161.
38. Limmroth V, Katsarava Z. Medication overuse headache. Curr Opin Neurol 2004 Jun;17(3):301-6.
39. Fritsche G, Diener HC. Medication overuse headaches -- what is new? Expert Opin Drug Saf 2002 Nov;1(4):331-8.
40. Katsarava Z, Diener HC, Limmroth V. Medication overuse headache: a focus on analgesics, ergot alkaloids and triptans. Drug Saf 2001;24(12):921-7.
41. Katsarava Z, Fritsche G. Gordian knot: medication overuse headache. Schmerz 2004 Oct;18(5):421-3.
42. Diener HC, Katasarva Z. Analgesic/abortive overuse and misuse in chronic daily headache. Curr Pain Headache Rep 2001 Dec;5(6):545-50.
43. Katsarava Z, Limmroth V, Finke M, Diener HC, Fritsche G. Rates and predictors for relapse in medication overuse headache: a 1-year prospective study. Neurology 2003 May 27;60(10):1682-3
44. Fritsche G, Eberl A, Katsarava Z, Limmroth V, Diener HC. Drug-induced headache: long-term follow-up of withdrawal therapy and persistence of drug misuse. Eur Neurol 2001;45(4):229-35.
45. Diener HC, Limmroth V. Medication-overuse headache: a worldwide problem. Lancet Neurol 2004 Aug;3(8):475-83.
46. Diener HC, Katsarava Z. Medication overuse headache. Curr Med Res Opin 2001;17 Suppl 1:s17-21.
47. Headache Classification Committee of the International Headache Society: Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8 (Suppl 7): 1-96.
48 Limmroth V, Kazarawa Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. Neurology. 2002;59:1011-4.
50. Katsarava Z, Fritsche G, Muessig M, Diener HC, Limmroth V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. Neurology. 2001;57:1694-8.
51. Manzoni GC, Torelli P for the International Headache Society. IHS classification: new proposals about chronic headache. Neurol Sci 2003;2:86-9.
52. Kavuk I, Yavuz U, Cetindere U, Agelink MW, Diener HC. Chronic headache: A focus on medication overuse. Eur J Med Res 2004;9:1-6.

Received: Oktober 18, 2004 / Accepted: November 22, 2004

Address for correspondence:
Ilker Kavuk, MD
Department of Neurology
University of Duisburg-Essen
Hufelandstr. 55
D-45122 Essen, Germany
Tel.: +49-201-7232461
Fax: +49-201-7235901
E-mail: ilker.kavuk@uni-essen.de