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Medication Overuse Headache

A Focus on Analgesics, Ergot Alkaloids and Triptans

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Contents

Abstract

Medication overuse headache (MOH, formerly known as drug-induced headache) is a well known disorder following the frequent use of analgesics or any other antiheadache drug including serotonin 5-$HT_{1B/D}$ agonists (triptans).

Recent studies suggest clinical features of MOH depend on the substance class that has been overused. The delay between the frequent intake of any antiheadache drug and daily headache is shortest for triptans (mean1.7 years), longer for ergot alkaloids (mean 2.7 years) and longest for analgesics (mean 4.9 years).

Treatment includes withdrawal followed by structured acute therapy and initiation of specific prophylactic treatment for the underlying primary headache. The relapse rate within 6 months after successful withdrawal is about 30% and increases steadily up to 50% after 5 years.

First described in 1951 by Peters and Horton,[1] medication overuse headache (MOH) has become a well characterised disorder[2,3] and a growing problem all over the world. In 1988 the International Headache Society (IHS) defined drug-induced headache by the following criteria: (i) headache appearing at least 15 times per month; (ii) regular intake of analgesics or ergot alkaloids; and (iii) successful treatment by withdrawal therapy.[2] The term drug-induced headache will be replaced by MOH in the new IHS classification which is expected to come into place mid to end of 2002, hence this latter term will be used in this article.

Until the mid-1990s MOH was only observed following the overuse of analgesics (mostly combined with substances such as codeine, caffeine or barbiturates) or ergot alkaloids. During the last 10 years serotonin 5-$HT_{1B/D}$ agonists (triptans) have been introduced into migraine therapy. The triptans have become popular due to their efficacy and low rate of adverse events. Recent observations now suggest that the frequent use of triptans may also lead to the development of MOH, with a different spectrum of clinical features.[4,5] It should be noted that the definition and clinical criteria of MOH by the IHS Classification Committee in 1988 was

based on experience with analgesics and ergot alkaloids only, and does not specify clinical features of triptan-induced headache.

This article summarises the current knowledge about MOH, its clinical features including those not covered by the definition of the IHS, critical monthly dosages and critical intake duration with regard to each group of substances.

1. Epidemiology

Epidemiological studies on the consumption of analgesics in the general population clearly indicate that antiheadache drugs are widely overused all over the world, in first as well as third world countries.[6-11] According to these surveys, 1 to 3% of the general population take analgesics on a daily basis and up to 7% have reported taking analgesics at least once a week.[12,13] There are only a few studies available that report on the incidence and prevalence of MOH in the general population. In a recent Spanish population-based study, about 1% of the general population experienced chronic daily headache combined with overuse of antiheadache drugs.[6] Another epidemiological study in a population of elderly (≥65 years) Chinese individuals revealed a prevalence of 3.9% of chronic daily headache in combination with analgesic overuse.[7] Studies on incidence and prevalence of MOH among patients with headache, however, were mostly conducted in or from specialised headache centres and observed that up to 10% of their patients with headache fulfilled the criteria of MOH.[8-10] A survey among 174 general practitioners in the US further suggests that MOH has become the third most common cause of headache after migraine and tension type headache.[11]

The majority of published epidemiological studies have investigated MOH following the overuse of analgesics or ergot alkaloids, according to the IHS criteria from 1988. In the last few years, however, triptans have become widely used, because of their efficacy and low incidence of adverse effects, and overuse has been observed. There are only a few studies that address the problem of triptan overuse. A study based on the prescription register in Denmark revealed the prevalence of sumatriptan use in the Danish population for 1995 to be 0.78%. Among users, up to 5% overused sumatriptan on a daily basis.[14] Evers et al.[15] found that 4.7% of 320 patients taking sumatriptan overused the drug by taking it at least every other day.[15] Data regarding the epidemiology of overuse of the other newer triptans (zolmitriptan, naratriptan, rizatriptan, eletriptan and almotriptan) are not yet available.

There is no doubt that MOH has become a major health problem in many countries. The fact that current epidemiological data on the prevalence and incidence are scarce calls for more population-based studies on MOH covering the overuse of all classes of antiheadache drugs, including all the newer triptans.

2. Clinical Features

Clinically, MOH has been defined by the Classification Committee of the IHS as a chronic holocranial, diffuse, dull headache, sometimes of pulsating character, without associated symptoms.[2] Ergotamine-induced headache, however, is described clinically as a diffuse and pulsating headache.[2] Again, these features were published in 1988 and were based on experience with analgesics and ergot alkaloids.

Diener and Dahlöf[16] performed a meta-analysis of 29 studies including 2612 patients with MOH. Patients with migraine represented the largest subgroup (65%), followed by patients with tension-type headache (27%), and patients with the co-occurrence of migraine and tension-type headache or other headaches (8%). More women than men reported MOH (3.5 : 1). When MOH was diagnosed, patients had a history of primary headache of a mean duration of 20.4 years. The mean duration of drug overuse was 10.3 years and the mean duration of daily headache was 5.9 years.[16]

It is now clear that all members of the triptan family can contribute to MOH. The first cases of sumatriptan-induced headache were observed in patients who had a history of ergotamine abuse and had switched to sumatriptan.[4,17] However, soon after this, *de novo* cases were also reported.[18-20]

Recently, patients who developed MOH following overuse of naratriptan and zolmitriptan have been reported.[5] Because of the delay between frequent intake of triptans and the development of MOH, it is likely that similar cases will be observed in the future with the newer triptans (eletriptan, frovatriptan and almotriptan).

Our most recent prospective study investigated the characteristics of MOH with regard to different drugs.[21] In this study 96 patients with MOH underwent inpatient withdrawal from their medication. Success of withdrawal from therapy was assessed after 1 month in a follow-up examination, and was defined according to the IHS criteria as no headache at all or an improvement of more than 50% in terms of headache days. As in most previous studies, the majority of our patients were female (female to male ratio of 4 : 1). 71% of patients reported migraine as their primary headache, 14% reported tension-type headache and 15% reported a co-occurrence of migraine and tension-type headache. Patients had a history of primary headache of a mean duration of 22 years, the mean duration of drug overuse was 6.5 years. 48% of 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, was more common by far than overuse of ergotamine. This might reflect the fact that, despite high acquisition costs, triptans have become widely used (and overused), and suggests that triptans are about to become the most important cause of MOH.

Unlike patients with MOH following ergotamine or analgesic overuse, patients with migraine (but not patients with tension-type headache) with triptan-induced headache did not describe the typical tension-type daily headache. Their headaches were described as a migraine-like daily headache (unilateral, pulsating with autonomic disturbances) 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 ergot alkaloids (2.7 years) and longest for analgesics (4.8 years). According to this, the intake frequency (single doses per month) was lowest for triptans (18 single doses per month), higher for ergot alkaloids (37 single doses per month) and highest for analgesics (114 single doses per month) [table I]. Hence, triptans do not only cause MOH with a different spectrum of clinical features, but are associated with a faster onset of MOH and with lower monthly drug doses, when compared with other substance groups used in the treatment of headache.

3. Pathophysiology

The pathophysiology of MOH is yet to be elucidated. Different mechanisms may contribute to the overuse of antiheadache drugs, and consequently to the transition from the original headache to MOH. It has been shown that patients with migraine and tension-type headache have a higher potential for MOH.[22] In contrast, patients with cluster headache seldom develop MOH, despite the frequent use of analgesics or ergot alkaloids.[16] Also, patients with other painful disorders (e.g. rheumatoid arthritis) do not develop MOH despite regular use of analgesics.[23] Interestingly, patients with a past history of migraine develop MOH after regular analgesic use for treatment of other painful diseases.[22] This finding suggests a genetic determination appears to be important.

Many antiheadache therapies contain drugs with psychotropic effects such as caffeine, codeine or barbiturates. Caffeine, for example, has been shown to act synergistically with analgesics,[24,25] and its effects include: increased vigilance; relief of fatigue; and improved performance and mood. As a result of these effects, during caffeine withdrawal, patients experience symptoms such as restlessness, irritability, nervousness and caffeine withdrawal headache.[26,27] The withdrawal headache may last for several days, which encourages the patient to reinstate regular drug intake. A recent international consensus paper on the dependence potential of caffeine concluded that there is a lack of evidence for caffeine playing a distinctive role in the development of MOH. Withdrawal head-

Table I. Pharmacological features from 96 patients with medication overuse headache (MOH) following the overuse of different antiheadache drugs[21]

Drug	Patients [no. (%)]	Mean duration of regular drug intake (mean ± SD) [years]	Mean frequency of drug overuse (mean ± SD) [doses/mo]	Mean monthly doses (mg)[a]
Analgesics	46 (48)	4.8 (4.9)	113.9 (63.5)	
Analgesics[b]	9 (9)	5.2 (5.0)	74.4 (47.5)	37 000
Analgesics[b] + caffeine	25 (26)	5.4 (5.1)	135.1 (57.9)	48 774
Analgesics[b] + codeine	4 (4)	5.5 (7.0)	129.0 (101.0)	72 550
Metamizol	2 (2)	2.3 (1.9)	34.5 (14.8)	17 250
Opioids	6 (6)	2.2 (2.1)	107.5 (52.3)	7 062
Triptans	38 (40)	1.7 (3.3)	18.6 (7.6)	
Sumatriptan	12 (13)	2.4 (3.1)	20.1 (8.3)	1 612
Zolmitriptan	20 (21)	1.7 (3.8)	18.4 (7.5)	46
Naratriptan	5 (5)	0.7 (1.3)	16.5 (7.8)	59
Rizatriptan	1 (1)	0.3 (ND)	15.0 (ND)	150
Ergot alkaloids	12 (13)	2.7 (2.0)	36.7 (18.1)	53

a Single doses for analgesics 500mg, sumatriptan 100mg, zolmitriptan 2.5mg, naratriptan 2.5mg, rizatriptan 10mg, ergot alkaloids 2mg, metamizol 500mg.

b Nonsteroidal anti-inflammatory drugs and metamizol.

ND = no data; **SD** = standard deviation.

ache, however, may occur if patients ingested caffeine daily at levels of at least 15 g/month.[28]

Administration of codeine, and other opioids, may also lead to physical dependency.[29-30] Rebound headache may be another factor. Medication withdrawal triggers the next headache, which in turn leads to the intake of the next dose of headache medication. This may initiate the cycle resulting in more frequent drug use, and consequently in MOH.

In our studies we observed that some patients who overused triptans did not develop a holocranial tension-type headache, but rather a migraine-like daily headache (called transformed migraine in the US). Furthermore, up to 20% of all triptan overusers developed an increase of migraine frequency without a daily occurring headache.[5,21] This increase might reflect a pre-condition of MOH with daily migraine-like headache. It is tempting to speculate about the underlying pathophysiology of triptan-induced MOH and the different clinical features in triptan overusers. One theory relates to the fact that zolmitriptan, naratriptan and rizatriptan in particular (triptans that are able to cross the blood-brain barrier easily), but not sumatriptan (which hardly crosses the blood-brain barrier) predominantly cause a migraine-like daily headache.[5] This indicates the involvement of central mechanisms. Furthermore, these patients mostly present with mild forms of autonomic disturbances such as nausea and photophobia/phonophobia as well, further supporting the concept of a central origin.[5] The new triptans exhibit not only a higher affinity but also a higher intrinsic activity at the 5-$HT_{1B/1D}$ receptors.[31] Whether this is an important aspect for the faster development of MOH caused by triptans relative to analgesics and ergot alkaloids or the low dosages at which triptans appear to cause MOH remains to be determined. Another important aspect for the development of MOH by the newer triptans might be the improved profile of adverse events. This improved safety profile may lead to an increase in drug intake bearing the danger of faster and less controlled usage. Further research is required to elucidate potential differences in mechanisms of the various triptans in MOH.

4. Management

Complete drug withdrawal is the treatment of choice for MOH. However, the discontinuation of any overused antiheadache drugs is accompanied by withdrawal symptoms. Symptoms include withdrawal headache, nausea, vomiting, arterial hypo-

tension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness, and last for 2 to 10 days.[3] The intensity of withdrawal headache increases on days 2, 3 and 4 and peaks again by the sixth to eighth day after withdrawal.[16] Some headache centres recommend the avoidance of replacement therapy during the first days of withdrawal, with the intention of reversing the conditioning response learned previously.[32] Most headache centres, however, treat withdrawal symptoms with nonsteroidal anti-inflammatories or with corticosteroids.[16]

Data regarding duration and clinical features of withdrawal from antiheadache drugs are scarce. There are a small number of older studies that have reported the symptoms of withdrawal from ergot alkaloids or combined analgesics only,[3] but there is a paucity of data describing the clinical features of withdrawal following the overuse of different triptans. In the only published report, withdrawal from sumatriptan has been suggested to be less severe than from analgesics.[33]

In a recently completed study in 96 patients who underwent standard inpatient withdrawal we prospectively investigated the duration as well as clinical features of withdrawal headache with regard to different antiheadache drugs including all the newer triptans.[34] In this study withdrawal from triptans was clearly shorter and less severe when compared with withdrawal from ergot alkaloids or analgesics, confirming the previous observation.[33]

Withdrawal therapy is performed differently depending on the drug being overused. A consensus paper by the German Migraine and Headache Society recommends outpatient withdrawal for highly motivated patients who did not take barbiturates or hypnosedatives (tranquillisers) in combination with analgesics. Patients overusing hypnosedatives, compounds containing codeine or barbiturates, or in whom withdrawal as outpatients has failed or in those patients who have a high depression score (≥20 points on Hamilton depression rating scale) should be considered candidates for inpatient treatment.[35]

Several treatment recommendations have been proposed for the acute phase of withdrawal in order to improve withdrawal symptoms. In an open-label study of 30 patients, valproic acid (sodium valproate) has been shown to have beneficial effects in the prophylactic treatment of chronic daily headache complicated by excessive analgesic intake.[36] A recently conducted open-label trial of 400 patients suggested that cortisone effectively reduces withdrawal symptoms including rebound headache in patients overusing a number of different headache drugs.[37] Sumatriptan has been shown to be effective in the treatment of ergotamine withdrawal headache – a double-blind study conducted in 11 patients reported a single subcutaneous dose of sumatriptan was more effective than placebo.[38] And finally, a randomised study has demonstrated that naproxen was more effective in the treatment of ergotamine withdrawal symptoms in 22 patients than symptomatic treatment with antiemetics and analgesics.[39]

In addition to the discontinuation of antiheadache drugs and replacement therapy, prophylactic treatment of the primary headache should be initiated. Interestingly, the effect of prophylactic treatment fails as long as the patient continues the overuse of antiheadache drug.[40] Consequently, many patients respond better to prophylactic treatment after drug withdrawal of the overused drug, despite the prophylactic drug initially appearing to be ineffective.[16]

Following withdrawal therapy, patients should complete a headache diary and be monitored every 3 months for the first year. Those patients who had reported tension-type headache or a co-occurrence of migraine and tension-type headache have a higher risk of relapse of MOH. These patients should be instructed precisely how to use their antiheadache drugs (no antimigraine drug for other nonmigraine headaches).

As a result of recent studies on MOH (see sections 1 and 2) it must be emphasised that it is crucial to restrict the number of doses per month for all antiheadache drugs to a maximum of 10 to 12 single doses. Since triptans are associated with a faster onset of MOH and with lower total doses

required, the number of single triptan doses should be limited to a maximum of 8 single doses per month. If patients need more doses than the proposed monthly limits, prophylactic medication should be initiated or changed. All combined antiheadache drugs, especially those containing barbiturates, codeine or hypnosedatives, should be avoided in all patients. Probably an early start of migraine prophylaxis, either by medical or behavioural treatment, can be a preventive measure to avoid MOH.[16]

5. Prognosis

Several studies have dealt with the long term outcome of patients with MOH after successful withdrawal therapy. However, most of these studies have several flaws. They are retrospective, and were performed in the 1980s or early 1990s evaluating the treatment of MOH following the overuse of analgesics or ergot alkaloids only. After 6 months relapse-free rates of about 70% were reported.[16,41] Two further studies covered observation periods of 9 and 35 months.[42,43] The relapse-free rates in these studies were 60 and 73%, respectively. A long term (5 years) follow-up study, however, found a relapse rate of 40%.[44] The recent long term (4 years) retrospective follow-up study performed by our group revealed a higher relapse rate of 48%.[45]

Predictors for relapses after successful withdrawal therapy remain difficult to analyse. Two aspects have been reported to be important: (i) the type of primary headache (patients with tension-type headache or co-occurrence of migraine and tension type headache have a higher relapse risk)[43,44] and (ii) the duration of regular drug intake (a longer duration of regular drug intake is also associated with a higher relapse risk).[43,46] These aspects, however, could not be confirmed in a recent study by our group.[45] Interestingly, in this study patients overusing triptans presented a significant lower relapse rate when compared with patients overusing other drugs.

Since the predictors for high relapse rates are not fully revealed, further prospective long term follow-up studies are needed, especially with the focus on newly developed triptans.

6. Conclusions

Epidemiological studies suggest that analgesic overuse and MOH are growing problems all over the world. Since 1993, following the approval of sumatriptan, the triptan family has become widely used and overused, consequently leading to an increasing number of patients suffering from triptan induced headache. Recent studies further indicate that a regular intake of triptans may lead to MOH faster and with the lower monthly dosages, compared to ergot alkaloids and analgesics. Complete withdrawal from overused medication is the treatment of choice for MOH. The withdrawal from triptans, however, is easier and shorter, compared with other headache drugs. More epidemiological and clinical studies are necessary to determine the critical monthly dosages, clinical features and predictors of relapse.

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