ABSTRACT

Use of medications more than 15 times per month to treat acute migraine attacks may cause medication overuse headache, formerly referred to as drug-induced headache. Such headaches can be brought on by frequent use of combination analgesics, opioids, ergots, alkylamines, or triptans. While patients who overuse analgesics preparations without or with an opioid tend to develop chronic tension-type headaches, patients overusing triptans or ergots are prone to daily headaches with migraine characteristics. Treatment strategies for patients with medication overuse headaches involve careful drug withdrawal with structured acute therapy and initiation of prophylactic treatment. Symptoms of withdrawal can be treated with prednisone and, where available, intravenous acetylsalicylic acid.

**Epidemiology and Pathophysiology**

Medication overuse headaches were formerly called drug-induced headaches. According to the new IHS criteria, the MOH is a daily or near-daily headache. The key factor in the definition of MOH is that the patient has had daily or near-daily intake of headache medications for the previous 3 months. In fact, this medication overuse is thought to be the driving force behind the transformation from an episodic pattern of headache to a daily headache. Interestingly, the MOH occurs almost exclusively in those with primary headache disorders.

According to findings of A.I. Scher, R.B. Lipton, and W.F. Stewart (written communication), as well as other published research, the best epidemiologic studies of MOH, performed in Spain and the United States, estimate the prevalence of MOH at around 1% to 1.2% in the general population. In the headache treatment center setting, of course, the prevalence is...
much higher, with most centers estimating that MOH accounts for about 30% of their patient load.1 In absolute numbers, this translates to approximately 2.2 million people in the United States and 2.5 million in Europe who have MOH; for comparison, this number is higher than the total number of Parkinson’s disease and multiple sclerosis patients, combined, in Europe and the United States.

An informal meta-analysis of 29 studies includ-
ing 2612 patients with MOH has helped shed some light on the pathophysiology of the disease.1 This analysis showed that before onset of treatment, 65% of MOH patients had previously had migraine headaches, 27% had tension-type headache, and 8% had a combination of these or another type of headache. Thus, patients with primary migraine or tension-type headache seem most predisposed to MOH. As many neurologists realize based on clinical experience, patients with cluster headache rarely develop MOH, even if they have been injecting sumatriptan on a daily basis for 2 to 3 years. Further, patients taking repetitive dihydroergotamine (DHE),11,12 and cortisone.14 Many of the placebo-

Table 1. Relapse Rates After Withdrawal Therapy in Medication Overuse Headaches

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Relapse Rate</th>
<th>Study</th>
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<tbody>
<tr>
<td>At 6 months</td>
<td>30%</td>
<td>Linton-Dahlöf 2000</td>
</tr>
<tr>
<td>At 2 years</td>
<td>23%</td>
<td>Baumgartner 1989</td>
</tr>
<tr>
<td>At 3 years</td>
<td>20%</td>
<td>Dener 1992</td>
</tr>
<tr>
<td>At 4 years</td>
<td>48%</td>
<td>Frittsche 2001</td>
</tr>
<tr>
<td>At 5 years</td>
<td>40%</td>
<td>Schneider 1996</td>
</tr>
</tbody>
</table>

From a physiologic standpoint, both beta-blockers and opioids are known to be additive. The ergots may also induce a physical dependency, and even caffeine has a well-known tendency to induce headaches when withdrawn suddenly. These addictive properties all indicate the need for further research in the area of receptor sensitization and its role in headaches and MOH.

Although the meta-analysis described earlier indicated that women had more MOH than men (ratio of 3.5:1), this does not prove that women have a higher tendency to develop MOH, as this trial was not prospective. The mean duration of the primary headache was 20 years, while the average MOH patient had been taking drugs frequently for about 10 years and was currently taking 2.5 to 5.8 drugs simultaneously.

The Pharmacology of Overused Medications

In a prospective study of patients with MOH, researchers found that the type of medication being taken can influence the evolution of MOH development.4 In this study, 46 MOH patients taking anal-
gies has a mean intake duration of 4.8 years before presenting, while those taking ergots had a mean of 2.7 years and those taking triptans had a mean of 1.7 years. The intake frequency of these agents in MOH patients also varied considerably; analgesics were consumed at an average 114 doses/month, ergots at 37 doses/month, and triptans at just 18 doses/month. Thus, triptans—even at a dose of less than one per day—are capable of inducing MOH in a dramatically shorter period of time than either barbiturates or ergots. These findings apply to all triptans equally.

Clinical aspects of the MOH also seem to vary according to the medication overused. In the 69 patients who had migraine headaches originally, 11 went on to report an increased frequency, 9 reported transforma-
tion to daily migraine, and 49 reported development of daily tension-type headaches (TTH). In the 14 patients with combined migraine and TTH at the start, 3 developed daily migraine and 11 developed daily TTH. Finally, all 9 patients self-medicating for TTH went on to report daily TTH. Note that only those patients starting with a migraine headache went on to develop MOH with elements of migraine pain. The TTH patients, who were taking only combination analgesics, did not develop migraine-like daily MOH. Thus, the pathophysiologic mechanism for MOH is different for triptans and ergots than it is for anal-
gies. Apparently, daily intake of combination anal-
gies leads to headache resembling TTH while the daily intake of ergots or triptans leads to an increased frequency of migraine-like headaches.

Treatment of Medication Overuse Headache

Although randomized and placebo-controlled studies of treatment of MOH are rare, several general principles of management can be outlined. The first, and most important, step is that patients must be completely withdrawn from their headache medica-
tion. Second, they should be shifted to a highly struc-
tured acute therapy, with a tight restriction on the number of doses per week and month. Limiting the acute therapy to about 10 to 12 doses per month is one common standard. The ideal pharmacologic agents for MOH patients during this structured therapy is currently uncertain, and important questions such as whether a patient who had developed MOH related to triptans can (re)sume structured therapy with triptans is simply unknown at this point. Finally, most of these MOH patients will eventually require some form of headache prophylaxis.

In one of the few prospective studies of MOH patients, researchers recently evaluated headache intensity and duration during the withdrawal phase.17 Although patients who had been taking triptans showed a slight rebound effect in the first few days after withdrawal, these patients also had a quicker recovery and lower overall headache intensity than those patients taking ergots or analgesics (mean intensity at 14 days: triptans 0.08, ergons 0.4, and analgesics 0.9; P < 0.001). The overall duration was also significantly shorter in patients overusing triptans (2.9 days) versus those coming off ergots (5.7 days) or analgesics (8.2 days) (P < 0.001). Thus, withdrawal from triptans is less severe and less time consuming than withdrawal from ergots or analgesics.

Drugs employed in replacement therapy will vary between patients and depend in part on whether the withdrawal is handled on an outpatient or inpatient basis. Agents tested have included NSAIDs such as naproxen,19 repetitive dihydroergotamine (DHE),10 sumatriptan,15 and cortisone.14 Many of the placebo-

controlled trials in this area have involved naproxen. While the rationale for giving DHE to patients who have ergot-related MOH (or, similarly sumatriptan to patients with triptan-related MOH) is questionable, several authors have also tested this strategy. Recent findings with sumatriptan show promise and merit fur-

ther evaluation in placebo-controlled settings. A significant percentage of patients relapse after initially successful withdrawal therapy. A review of recent prospective or retrospective studies evaluating long-term follow-up in MOH reveals that although positive results can be expected with with-
drawal therapy (between 48% and 91% in a review of 23 papers), the relapse rate at various endpoints was high (Table 1).15,16 Evaluation of such long-term studies reveals several features that predict which patients will relapse into MOH. The main risk factors appear to be use of barbi-

turates or opioids and the presence of concomitant depression. In patients taking barbiturates, relapse rates of 100% have been reported, explaining why these patients in particular require special care and also why some countries, such as Germany, have banned barbitu-
rates from analgesic combination products.

A very recent prospective evaluation of long-term outcomes following withdrawal and treatment of patients with MOH reports that 31/80 (40%) of patients had begun to overuse medications again, and 28/80 (35%) had resulting MOH.16 Patients who had originally been taking triptans showed significantly less likely to suffer a relapse at 1 year (4/28, 14%) versus those who had been taking ergots (2/10, 20%) or analgesics (22/42, 52%) (P < 0.05). Migraine was also...
found to be a positive predictor for long-term treatment success, with only 12/22 MOH migraine patients having relapses versus 8/11 MOH patients with TTH (P < 0.005). The headache medications associated with the lowest risk of subsequent overuse and MOH relapse after discharge were the triptans, followed by single analgesics and combination analgesics (Table 2).

CONCLUSION

Based on the currently limited scientific database, clinicians should be aware that MOH is a frequent entity, especially in the headache clinic setting. All drugs used to treat migraine attacks can cause MOH. The more potent migraine medications are associated with a shorter time interval to development of MOH, with triptans and ergots inducing MOH more rapidly than analgesics. To reduce the incidence of MOH, clinicians should attempt to restrict the number of weekly or monthly doses of migraine drugs—even in those patients who do not currently have MOH. Prophylactic therapy should be instituted in patients with MOH to increase the chances of long-term success.

REFERENCES


Table 2. Which Headache Medications Are Associated With the Lowest Risk of Overuse or MOH Relapse After Withdrawal Treatment and Discharge!

<table>
<thead>
<tr>
<th>Headache Medication After Discharge</th>
<th>Single Analgesics</th>
<th>Combined Analgesics</th>
<th>Triptans</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 Months</td>
<td>N=52</td>
<td>N=8</td>
<td>N=24</td>
</tr>
<tr>
<td>Drug overuse</td>
<td>16 (31%)</td>
<td>7 (88%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Relapsed MCH</td>
<td>14 (27%)</td>
<td>7 (98%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>At 1 Year</td>
<td>N=40</td>
<td>N=12</td>
<td>N=20</td>
</tr>
<tr>
<td>Drug overuse</td>
<td>16 (38%)</td>
<td>8 (67%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Relapsed MCH</td>
<td>13 (31%)</td>
<td>8 (67%)</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>

P < 0.05

MOH = medication overuse headache

Adapted from Katsarava Z, Fritsche C, Finke M, Diener H. Clinical features of withdrawal headache and long-term follow-up after withdrawal from triptans in comparison to other antimigraine drugs. Presentation at: International Headache Congress 2001; July 1, 2001; New York, NY.