Acta neurol. belg., 2006, **106**, 43-51

Guidelines

Practical management of medication-overuse headache

Koen PAEMELEIRE[1,2], Luc CREVITS[1], Peter J. GOADSBY[2] and Holger KAUBE[2]

[1]Department of Neurology, Ghent University Hospital, Belgium ; [2]Headache Group, Institute of Neurology, University College London, United Kingdom

Abstract

Epidemiological studies suggest that medication-overuse as defined by the International Headache Society is extremely common in patients with chronic daily headache. If all medication-overuse produces medication-overuse headache (MOH) in headache patients, it would be the third most frequent form of headache, after tension-type headache and migraine. Treatment of MOH is hindered by the absence of placebo-controlled, double-blind, randomised clinical trials. Nevertheless, several headache centers worldwide have developed expertise in the treatment of this syndrome, and have been quite successful. Here, we summarize available data on MOH, including clinical features, drugs used in withdrawal, as well as withdrawal strategies that have been described in the literature. We also include a detailed description of an in-patient and out-patient withdrawal procedure, reflecting personal experience and opinion of the authors.

Key words : Chronic daily headache ; medication-overuse headache ; analgesia withdrawal ; dihydroergotamine ; guidelines.

Introduction

Epidemiological data suggest that the chronic headache (CH) prevalence, as defined by the International Headache Society (IHS), is between 2 and 5% of the adult population (Scher *et al.*, 1998 ; Pascual *et al.*, 2001 ; Lantéri-Minet *et al.*, 2003 ; Diener and Limmroth, 2004 ; Headache Classification Committee of the International Headache Society, 2004). CH is associated with the overuse of symptomatic medication in about half of these patients, such that the prevalence of CH subjects with medication overuse (MO) is around 1% (Diener and Limmroth, 2004), but may be up to 2% in the United States (Young, 2001). A definite diagnosis of medication-overuse headache (MOH) can only be made in retrospect, as the diagnostic criteria of the IHS for MOH (Table 1) include that headache has to resolve or revert to its previous pattern within 2 months after discontinuation of the overused drug(s). MOH is probably the third most frequent form of headache, after tension-type headache and migraine and the major avoidable cause of headache disability in the developed world (Pascual *et al.*, 2001). These patients present a syndrome characterized by the regular, dependable and predictable development of a headache within hours of the waning therapeutic effect of the last dose of medication, creating dependence on symptomatic medication (Williams and Stark, 2003). The syndrome has a peak prevalence in women in their fifties (Colas *et al.*, 2004), but has even been described in children (Von Korff *et al.*, 1995 ; Vasconcellos *et al.*, 1998). The headache can resemble chronic tension-type headache or chronic migraine (Pini *et al.*, 1996). Patients overusing triptans more likely describe a daily or near-daily migraine-like headache or an increase in migraine frequency. Most patients with MOH have a (near)-daily headache. Some patients have a predictable early morning headache (Zed *et al.*, 1999). These patients have furthermore become refractory to prophylactic medication, which contributes to a refractory headache cycle. Self imposed attempts at drug withdrawal often fail within the first 2-3 days due to an almost unbearable worsening of the headache and appearance of withdrawal symptoms such as nausea and autonomic symptoms. These withdrawal symptoms are generally relieved by further use of the analgesics in question, which give the patient the false impression that he or she is doing 'the right thing' (Linton-Dahlof *et al.*, 2000). Overuse of symptomatic headache medication may have several other deleterious health consequences, such as analgesic nephropathy, (subclinical) ergotism, hepatotoxicity and NSAID gastropathy.

The mechanism of the development of MOH is at present unknown but it appears to occur mainly in patients with an underlying primary headache disorder, especially (episodic) migraine (Bahra *et al.*, 2003 ; Zwart *et al.*, 2003). Other primary headaches associated with MOH are chronic tension-type headache (± evolving form episodic tension-type headache), hemicrania continua and

Table 1

Diagnostic criteria (IHS) for medication-overuse headache

Ergotamine-OH	Triptan-OH	Analgesic-OH	Opioid-OH	Combination medication-OH
A. Headache present on > 15 days/month, fulfilling criteria C and D				
And with ≥ 1 of the following characteristics : 1. Bilateral 2. Pressing/tightening quality 3. Mild or moderate intensity	And with ≥ 1 of the following characteristics : 1. Predominantly unilateral 2. Pulsating quality 3. Moderate or severe intensity 4. Aggravated by or causing avoidance of routine physical activity 5. Associated with ≥ 1 of the following : a) nausea and/or vomiting b) photo- and phonophobia	And with ≥ 1 of the following characteristics : 1. Bilateral 2. Pressing/tightening quality 3. Mild or moderate intensity		And with ≥ 1 of the following characteristics : 1. Bilateral 2. Pressing/tightening quality 3. Mild or moderate intensity
B : Ergotamine intake on ≥ 10 d/month on a regular basis for ≥ 3 months	**B** : Triptan intake on ≥ 10 d/month on a regular basis for ≥ 3 months	**B** : Intake of simple analgesics on ≥ 15 d/month for > 3 months	**B** : Opioid intake on ≥ 10 d/month for > 3 months	**B** : Intake of combination medications on ≥ 10 d/month for > 3 months
C : Headache has developed or markedly worsened during ergotamine overuse	**C** : Headache frequency has markedly increased during triptan overuse	**C** : Headache has developed or markedly worsened during analgesic overuse	**C** : Headache has developed or markedly worsened during opioid overuse	**C** : Headache has developed or markedly worsened during combination-medication overuse
D : Headache resolves or reverts to its previous pattern within 2 months after discontinuation of the causal drug				

new daily persistent headache (Schnider *et al.*, 1994). We have recently described that even cluster headache patients may develop MOH, especially those with a personal and/or family history of migraine (Paemeleire *et al.*, 2004). Also SUNCT may be associated with MOH (unpublished observation). The following (categories of) drugs are associated with MOH (Table 1) : simple analgesics (acetaminophen, and less frequently acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs)), caffeine, opioids (De Marinis *et al.*, 1991 ; Ziegler, 1994), combination analgesics, ergotamine (Ala-Hurula *et al.*, 1982), triptans (Kaube *et al.*, 1994a ; Evers *et al.*, 1999) and barbiturates (especially in the USA and Canada) (Loder and Biondi, 2003). Retrospective data suggest that the time between the frequent intake of any anti-headache drug and the development of daily headache is shortest for triptans (mean 1.7 years), longer for ergot alkaloids (mean 2.7 years) and longest for analgesics (mean 4.9 years) (Limmroth *et al.*, 2002). It was also concluded that the mean critical monthly intake frequency was the lowest for triptans (18 single doses per month) in comparison with ergots and analgesics.

Initiation of and sustaining the overuse of medication involve psychological and behavioral factors, such as cephalgiaphobia, anticipatory anxiety or obsessional drug-taking (Saper *et al.*, 2005). Cross-sectional data suggest an association between behavior of substance dependence and probable MOH (Fuh *et al.*, 2005), but there is no proof at present of a causal relationship. Interestingly, a recent PET study showed persistent orbitofrontal cortex hypofunction 3 weeks after withdrawal in patients with MOH and a history of episodic migraine (Fumal *et al.*, 2006). Hypoactivity of the orbitofrontal cortex might favour ongoing medication overuse in MOH patients. We are looking forward to a complimentary PET study performed after a longer interval following withdrawal to exclude persistent metabolic effects of previously overused drugs, to corroborate the suggestion of an underlying psychobiological trait predisposing MOH patients to substance dependence. Most patients should not be treated on psychiatric wards or in detoxification facilities. Psychiatric co-morbidity to migraine, such as depression and anxiety, is however associated with MO (Radat *et al.*, 1999) and a predictor of intractability.

The primary measure in alleviating MOH is to stop the offending drug. Discontinuation usually results in the development of withdrawal symptoms and a period of increased headache, preceding improvement of headache. Withdrawal symptoms are commonly experienced in the first 4 days (Mathew *et al.*, 1990) and may persist up to 2-3 weeks (Krymchantowski and Barbosa, 2000). Exacerbated headache, nausea and vomiting, agitation, restlessness and sleep disorder, diarrhoea,

tremor and rarely seizures may occur. Retrospective data showed that the duration of the withdrawal headache was shorter in patients overusing triptans (4.1 days), than in patients with overuse of ergots (6.7 days) or analgesics (9.5 days) (Katsarava *et al.*, 2001a ; Katsarava *et al.*, 2001b). It may take up to 6 weeks to reverse the effects of MO (Mathew *et al.*, 1990). Other authors reported up to 6 months omission of symptomatic medications are necessary until the almost daily headaches seize (Warner, 1998). Until now no placebo-controlled, double blind, randomized, clinical trials give guidance on the treatment of MOH. None of the studies reported to date provide *class I* evidence. Therefore, no formal recommendations for optimal therapy can be made. Thus, the following recommendations are based on the best available evidence and personal experience and opinion of the authors.

In-patient or out-patient treatment ? Abrupt versus slow withdrawal ?

Highly motivated patients with MOH, using moderate amounts of agents, other than opioids, barbiturates or benzodiazepines, can be treated on an out-patient basis, and may have as good outcomes as those with in-patient care (Freitag *et al.*, 2004), if adequate support from primary health care providers and others is readily available (Zed *et al.*, 1999 ; Krymchantowski and Moreira, 2003). Several factors may determine the necessity of an in-patient programme (Freitag *et al.*, 2004) and are summarized in Table 2. A significant withdrawal is expected with barbiturates, benzodiazepines, and opiates, as well as in those with a very high degree of overuse of other drugs.

Abrupt withdrawal is often the treatment of choice (Hering and Steiner, 1991) and is preferred by the authors, as it is associated with a shorter duration of suffering for the patient, and also with reduced admission time and health care costs in in-patients. No prospective trials have however compared gradual with abrupt drug withdrawal. Patients overusing barbiturates or opioids should have these agents gradually tapered (Zed *et al.*, 1999), either quickly during an admission, or slowly as an out-patient. Patients chronically using daily opioids during mid-to-late pregnancy must continue daily opioids because of the risks of fetal mortality and premature labor associated with intrauterine fetal opioid withdrawal (Brandes and Marcus, 2004).

Table 2

Criteria in the decision between in- and out-patient approaches for analgesia withdrawal in patients suffering from MOH

OUT-PATIENT	IN-PATIENT
Motivated patient Mild-moderate overuse	Drugs (opioids, barbiturates) Status migrainosus Severe vomiting/dehydration Social situation (single parent) Previous failed as out-patient Psychiatric co-morbidity Medical co-morbidity Fear of drug interactions

Drugs used in analgesia withdrawal

1. Dihydroergotamine

Intravenous (IV) dihydroergotamine (DHE), according to the original three and a half day protocol described by Raskin (1986), remains the treatment of choice for in-patients. In-patient monitoring is necessary if DHE is used IV on more than 2 days (Quality Standards Subcommittee of the American Academy of Neurology, 1995). Meanwhile, an ambulant in-hospital IV therapy has been described (Robbins and Remmes, 1992). DHE has been shown to be efficacious, shortening hospital stay and reducing analgesic withdrawal symptoms. The protocol consists of IV DHE every 8 hours in combination with an anti-emetic to control nausea (Table 3). Pre-treatment with peroral (PO) or per rectum (PR) domperidone (10-20 mg or 60 mg respectively) is necessary. If domperidone is not effective, IV metoclopramide 10 mg or IV granisetron 1 mg may be used. Common side effects of DHE are nausea, vomiting, abdominal pain, diarrhoea, leg cramps and paresthesias. There is a small risk of peripheral vasospasm as well as myocardial and intestinal ischemia. Bradycardia and tachycardia have been observed. Myocardial infarction is rare. Repeated high dosage may cause ergotism with gangrene and confusion. Pleural, peritoneal, and heart valve fibrosis have been described with prolonged excessive use. In a retrospective analysis of data for 300 patients with refractory headache who were treated with IV DHE, side effects were reported in about 50% of the patients (Silberstein *et al.*, 1990). They consisted primarily of nausea (about one third of patients), and between 5 and 10% of patients reported tightness and burning, leg cramps, vomiting and increased blood pressure. Contra-indications are vascular disease (peripheral, coronary and cerebral vascular disease, Raynaud's phenomenon, temporal arteritis), hepatic and renal impairment, sepsis, severe or inadequately controlled hypertension, hyperthyroidism, (imminent) pregnancy and breastfeeding, and porphyria.

2. Corticosteroids

There are some data available on the use of a short course of oral corticosteroids in the initial

Table 3

Repetitive IV dihydroergotamine (DHE) protocol

Number	Time (h)	Dose DHE[1]	Cumulative Dose
1	0	0,5 mg	0,5 mg
2	8	0,75 mg	1,25 mg
3	16	1 mg	2,25 mg
4	24	1 mg	3,25 mg
5	32	1 mg	4,25 mg
6	40	1 mg	5,25 mg
7	48	1 mg	6,25 mg
8	56	1 mg	7,25 mg
9	64	1 mg	8,25 mg
10	72	1 mg	9,25 mg

[1]Each dose is preceded by domperidon administration (10-20 mg PO or 60 mg PR).

phase of medication withdrawal. Two large open label studies were performed in the out-patient setting, using a 6-day tapering course of prednisone (60 mg/d for 2 days, 40 mg/d for 2 days, 20 mg/d for 2 days) plus ranitidine (300 mg/d for 6 days) immediately after sudden medication withdrawal (Krymchantowski and Barbosa, 2000 ; Krymchantowski and Moreira, 2003). The authors observed a lack of withdrawal symptoms in the majority of patients, and a significant reduction in headache severity and frequency. No significant side effects or steroid withdrawal symptoms were reported. A small placebo-controlled, double blind and randomized pilot study confirming the beneficial effect of oral prednisone, using a fixed 5 days oral course of prednisone 100 mg/d (Pageler *et al.*, 2004). We suggest the use of methylprednisolone 64 mg/d for 5 days in combination with ranitidine 300 mg/d in the Belgian context. The use of other parenteral corticosteroids, including dexamethasone and hydrocortisone has also been described for in-patients (Silberstein and Lipton, 2001). Corticosteroid therapy should not be tapered after a short course. The use of steroids is limited by a long list of contra-indications, as well as fear of steroids.

3. Neuroleptics

Chlorpromazine is considered the most effective neuroleptic for head pain in acute migraine (Evans and Young, 2003). It has marked sedating and antiemetic effects. The recommended dose in withdrawal is 12.5-25 mg (up to 50 mg in refractory cases) 3-4 times daily (IV, IM, PO). The maximum recommended 24 hour IM/IV dose is 150 mg (Evans and Young, 2003). Side effects are usually mild. Due to its hypotensive properties, patients should remain supine and the blood pressure should be monitored for 30 minutes after an IM (or IV) injection. Side effects include extrapyramidal symptoms, interference with temperature regulation, neuroleptic malignant syndrome, anticholinergic effects, cholestatic jaundice, blood dyscrasias, drowsiness, convulsions and cardiovascular symptoms (hypotension, tachycardia, QTc prolongation, arrhythmia). Accordingly, several contra-indications have to be observed. Chlorpromazine is available as a cheap extemporaneous (magistral) PO preparation on the Belgian market. Chlorpromazine intramuscular (IM) or IV is not on the Belgian market as a specialty drug, but can be ordered through the hospital pharmacy in France (Largactil® 25 mg). The authors do not recommend the use of droperidol (higher risk of QTc prolongation and tardive dyskinesia) or prochlorperazine (high incidence of extrapyramidal side effects).

4. Non steroidal anti-inflammatory drugs

A transitional oral therapy with long acting NSAIDs such as naproxen has been suggested in the withdrawal of analgesics, both in the in- and out-patient setting, provided these agents are not already being overused. NSAIDs have also been used parenteral in the in-patient setting, although there is no evidence to support this is more effective than oral treatment. Dosing and duration of treatment with NSAIDs are based on clinical judgement of the severity of the withdrawal headache (Mathew, 1987 ; Zed *et al.*, 1999). We generally recommend oral naproxen at a dose of up to 1000 mg per day, either as 2 times 500 mg or as 3 times 250 mg per day with an optional extra 250 mg for severe exacerbations. IV ASA 1000 mg is the preferred parenteral drug and may be used up to 3 times daily (with a gap of at least 4 hours between each dose). It may also be used by IM administration. Gastric protection may be indicated and there are several well known contra-indications. NSAID have been combined with low dose amitriptyline (10 mg) (Suhr *et al.*, 1999) and tizanidine (Smith, 2002) in the out-patient withdrawal of analgesics.

5. Sodium valproate

IV sodium valproate has been suggested as an alternative if DHE is contra-indicated, not tolerated, or causes adverse events. In a small study, using a loading dose of 15 mg/kg over 30 minutes, followed by 5 mg/kg every 8 hours over 15 minutes, improvement in headache was reported by 80% of the patients treated (Schwartz *et al.*, 2002). A very low incidence of adverse events has been reported. Nevertheless, we would rather recommend using a loading dose of 10 mg/kg, as suggested in the package insert. Liver function tests should be monitored before and after starting therapy. We also recommend assessing full blood count and pancreatic function, because of the risk of thrombocytopenia and pancreatitis.

6. Lidocaine

IV lidocaine has been used as an adjunct in acute withdrawal of patients overusing mainly high doses of opioids (Kaube *et al.*, 1994b ; Hand and Stark, 2000 ; Williams and Stark, 2003). Lidocaine was used at a dose of 2 mg/min for 7 to 10 days. Breakthrough headache was treated with naproxen or a triptan in patients with a history of episodic migraine. Side effects were symptomatic hypotension, hot flushes, and diarrhoea, as well as painful IV sites and IV site infections. None resulted in termination of treatment. We reserve lidocaine as a last resort for intractable headache. Prior to starting the treatment, patients should have a resting electrocardiogram (ECG) and assessment of renal and liver function. Hypokalemia and other electrolyte disturbancs should be corrected prior to starting treatment. A fluid chart is kept rigidly to prevent dehydration. Continuous cardiac monitoring during infusion, as well as regular checks of blood pressure and heart rate are obligatory. Equipment for cardiopulmonary resuscitation must be available. The dose of lidocaine is escalated. We start with a dose of 1 mg/min for 6-8 hours, followed by 2 mg/min for 24 hours, followed by 3 mg/min for 24 hours, and finally we bring the dose further up to a maximum of 4 mg/min. The maximal rate in an individual patient is related to the patient's weight, at 3.4 mg/kg/h. This means that for a patient weighing less than 70 kg, the maximal dose of lidocaine is less than 4 mg/min! We use lidocaine continuously for a maximum of 7 days.

7. Others

The feasibility of analgesia withdrawal with only an anti-emetic, has been shown in hospitalized patients (Diener *et al.*, 1989). These patients suffered from intense withdrawal symptoms, including a massive increase in headache intensity, vomiting and insomnia. About half the patients were headache free on discharge. In our view, this approach is only an option in patients with very mild overuse, or those limited by contra-indications. Other authors have suggested using only rescue medication, such as NSAIDs (e.g. naproxen, unless previously overused), DHE or triptans (subcutaneous (SC) sumatriptan 6 mg) on a maximum of 2 occasions per week (Linton-Dahlof *et al.*, 2000 ; Warner, 2001). Finally, short-term treatment with oral triptans has been described in the outpatient setting in patients with a history of episodic migraine. Both naratriptan (Krymchantowski and Moreira, 2003) and sumatriptan (Drucker and Tepper, 1998) have been used for that purpose. However, triptans are an underestimated cause of MOH themselves and ergotamine-induced headache can be sustained by daily triptan intake (Catarci *et al.*, 1994). We do not recommend this option. IV tricyclic antidepressants (such as clomipramine) and acamprosate are used in withdrawal by some, but there are very limited published data (Lenarduzzi *et al.*, 1998).

Table 4

Suggested drug regimes for analgesia withdrawal

	Drug
First choice	Naproxen PO (OP) Dihydroergotamine IV (IP)
Alternatives	Methylprednisolone PO (OP) or IV (IP) Chloorpromazine IV (IP) Sodiumvalproate IV (IP)
Refractory patient	Lidocaine IV (IP)

IP = in-patient ; OP = out-patient ; PO = peroral ; IV = intravenous.

Specific withdrawal strategies (Table 4)

1. In-patient withdrawal

Patients are admitted to a neurology ward, for 7 to 10 days on average. Generally, this consists of a withdrawal period of up to 7 days with rescue medication, followed by a 3.5 day standard treatment with IV DHE if necessary. The patient is instructed and consented on the procedures, as well as on the use of drugs for unlicensed indications. We explain that during the washout period from the overused drug, headache may temporarily get worse before it gets better. A diary with hourly visual analogue scale rating of the headache is kept throughout the admission and also documents the treatment received. Vital parameters are regularly checked. We recommend patients to try to maintain a normal day-night cycle. Overused analgesics are generally completely stopped on day 1 of the admission. An acute withdrawal may be undesirable in some patients, including in those suffering from a cardiac or endocrine disorder. In such patients, the dose of the overused drugs may be halved first, and stopped completely a few days later if all goes well. If slower withdrawal is necessary, it is done on an out-patient basis. Important exceptions are the overuse of barbiturates and opioids. Management of butalbital withdrawal can be simplified by using a phenobarbital-loading protocol, taking advantage of the natural tapering by the drug's long half-life (Sullivan and Sellers, 1986 ; Loder and Biondi, 2003). Several strategies have been developed for opiate withdrawal treatment (Amato *et al.*, 2004). One option is to replace the overused opioid by a long-acting opioid, such as buprenorphine or methadone, and then slowly taper off this drug. Another more time efficient method for patients with mild to moderate overuse of opioids for headache, is the use of the α_2-adrenergic agonist clonidine if opioid withdrawal symptoms develop.

Depending on the dose, abrupt withdrawal may be possible, or the dose of the overused opiate(s) may be halved first and stopped completely a few days later if all goes well. If necessary, slower withdrawal of opiates is attempted on an out-patient basis. A baseline ECG should be obtained with regard to the likely use of clonidine (risk of bradycardia) of DHE. Clonidine is generally not started to *prevent* the development of withdrawal symptoms, but we have a low threshold to start it. Clonidine is started as soon as autonomic symptoms, such as sweating, diarrhoea and pupil dilation, develop. Worsening of headache alone is not an indication to start clonidine. Since benzodiazepines are not associated with MOH, we recommend an out-patient slow withdrawal. Some authors have suggested an approach with no rescue medication at all during the initial week. However, we allow patients to use 1 gram of IV ASA as a rescue medication, with a maximum of 3 times daily. A freshly prepared solution should be used within 15 minutes to avoid hydrolysis of the drug. The patients themselves decide on the timing of ASA, with a minimum of 4 hours between 2 doses. IV ASA 1 gram is given slowly over 5 minutes. An IV route is preferred because of nausea and to increase bioavailability. If the patient does not want an IV line, IM ASA or a PO NSAID (such as naproxen up to 1000 mg per day) are alternatives. If ASA/NSAIDs are contra-indicated, chlorpromazine may be used for pain, nausea and withdrawal symptoms. A treatment with DHE could also be started straight away. Patients may ask for chlorpromazine 12.5-25 mg up to 3-4 times daily. Chlorpromazine is furthermore sedating and other patients may use a single 12.5-25 mg dose (PO, IM) at night. If both ASA/NSAIDs and neuroleptics are contra-indicated, a triptan (SC sumatriptan 6 mg) can be considered for migrainous exacerbations, unless a triptan or ergot was previously overused. Patients additionally may use cold packs. Adequate hydration is helpful. We recommend drinking lots of fluid, to use a maximum of 2 cups of tea or coffee per day and to avoid alcohol completely. Patients are reassessed daily. If they are nauseous, either PO domperidone or IV metoclopramide is given. If there is a risk of dehydration, 2 liter IV fluid per day is given. A sleep disorder may respond well to a low dose of amitriptyline (as low as 10 mg at night). It seems that these patients are less able to tolerate sleep disturbance and insomnia is sometimes reported as a stimulus for recurrent headaches (Pini *et al.*, 1996). Exceptionally, PO zopiclon may be used if necessary when amitriptyline or chlorpromazine are contra-indicated. Opioid withdrawal symptoms can be treated with clonidine, either PO or by slow IV injection (Dalessio, 1991). We generally start with an oral dose of 3 times 25 μg per day. The dose is subsequently titrated up and down according to the evolution of the withdrawal symptoms. The drug must be withdrawn gradually to avoid a hypertensive crisis and rebound tachycardia. If patients still suffer from pain after 7 days, an IV treatment with DHE (Table 3) is proposed, according to the Raskin protocol (Raskin, 1986). including an initial dose escalation. Each dose of DHE is preceded by PO domperidone (10-20 mg) or PR (60 mg). If domperidone is not effective IV metoclopramide 10 mg is started. Each dose of DHE is dissolved in saline and infused over 1-2 hours. A gap of 7-8 hours is left between two consecutive DHE doses. If the patient is nauseous, the dose should not be escalated and should remain at the highest that the patient can tolerate in an 8 hourly regime until 9 mg ± 1 mg has been administered or 4 days have elapsed. The maximal dose of DHE is 11 mg in adults. After each dose side effects are assessed. An alternative to reduce possible nausea is to give the patient 3 mg in 500 mL saline (NaCl 0.9%) at a rate of 21 ml per hour for 3 days. In refractory cases of nausea or vomiting, IV granisetron (Kytril®) may be necessary. Leg cramps are a common side effects but deep venous thrombosis has not been reported. We recommend passive leg exercises and walking. Triptans may not be used 24 hours before until 24 hours after the treatment with DHE. We explain to patients that DHE may have a delayed effect (i.e. after the end of admission), that the effect of DHE may last up to 3 months and that it is our practice not to repeat DHE within 4 months. If DHE is contra-indicated or ineffective, IV chlorpromazine, IV methylprednisolone and IV sodium valproate are second line agents. Neuroleptics and steroids may also supplement DHE in refractory patients. IV lidocaine is an option for a small group of refractory patients, and there is limited data that suggests its use for patients with significant codeine-overuse. After or during withdrawal a preventive is started. Follow-up is very important, initially through their general practitioner, and with a return visit planned to the neurology out-patient clinic as well.

2. Out-patient Withdrawal

If an acute withdrawal is started at home, patients should receive a physician's certificate for sick leave for 7-10 days, otherwise they are unlikely to succeed (Linton-Dahlof *et al.*, 2000). Adequate support from the general practitioner is a prerequisite for success too. If overuse was limited, a rescue medication may not be necessary. Patients can use PO naproxen as a rescue medication, unless NSAIDs were previously overused. Naproxen 250 mg is given 2-3 times daily for 2 weeks, with an additional 250 mg tablet as a rescue medication. The maximum recommended dose for naproxen is 1 gram per day. As naproxen is also a short-term migraine preventive, it may be continued in this

way for up to 6 weeks in migraineurs. PO domperidone 20 mg is used for nausea. In patients with a history of episodic migraine, SC sumatriptan can be used a maximum of 2 times per week, if not previously overused. Guidelines for hydration are similar to the in-patient strategy. The potential benefit of adding a low dose of tizanidine (2-4 mg, taken at bedtime) to NSAIDs for withdrawal has to be confirmed. A low dose of amitriptyline (10-25 mg) at bedtime may be effective for sleep disturbances. An admission may be necessary if the patient develops dehydration or severe withdrawal symptoms. Evidence is accumulating for the safe use of a short course of PO corticosteroids as an alternative to NSAIDs, especially when the latter are contra-indicated. We suggest using methylprednisolone 64 mg/d for 5 days in combination with ranitidine 300 mg/d for 5 days. PO chlorpromazine may be used as an alternative in patients with contra-indications to NSAIDs. Rescue medications that can be administered by the general practitioner include IM/SC DHE, SC triptan or a shot of IM/IV steroids.

Additional measures

With regard to the possibility of hemicrania continua, all cases with chronic unilateral daily headaches should receive an indomethacin trial, preferably placebo-controlled. After withdrawal a preventive should usually be initiated, depending on the underlying primary headache. Placebo-controlled randomized clinical trials exist in this domain, for which the reader is referred to excellent reviews (Silberstein and Goadsby, 2002 ; Bigal *et al.*, 2004 ; Loder, 2004). Generally speaking, the authors prefer preventive monotherapy. One is reluctant to go back to previously failed preventives, unless they were used during MO. Acute therapy should also be initiated and limited to 6-8 days per month or 2 days per week. Patients are instructed that mild headaches should not be treated. The general rationale is that patients should not use the same drug as they previously overused. Assessment of behavioral and psychological co-factors in the development of MOH is essential. Psychiatric co-morbidity (such as depression, anxiety or substance dependence) should be treated separately. It has been suggested that a combination of pharmacologic and behavioral treatment, mainly relaxation, biofeedback, and stress-management, is more effective than drug therapy alone in the long-term management of MO (Grazzi *et al.*, 2002), however confirmation is required. Limited dietary changes should be suggested if relevant, including low caffeine and alcohol intake. Discontinuation of nicotine is encouraged, as well as regular sleep and meals. Aerobic exercise may be beneficial (Koseoglu *et al.*, 2003). Close follow-up of patients after withdrawal is necessary for the early detection of relapse. The risk of relapse is greatest in the first year after withdrawal and amounts to at least 50% 5 years after withdrawal. The relapse rate is highest in patients overusing opioids.

Prospects

Conservative extrapolation of epidemiological studies to the Belgian situation would suggest at least 100,000 people are suffering from CH with MO in Belgium. As in many countries, Belgium has only few resources dedicated specifically to this problem and many of these patients have given up seeking care from a physician. However, the authors advocate challenging the problem of MOH and recommend an in-patient or out-patient treatment depending on the situation. The protocols, described in this paper, are derived from a tertiary care centre (at the National Hospital for Neurology and Neurosurgery in London, UK), which specializes in headache treatment, and have been adapted to the Belgian situation. We recognize that protocols need to be adapted to the individual patient, but protocols are important for training purposes, as well as for achieving a high level of care.

Acknowledgements

This work was supported by a Horlait-Dapsens grant (Belgium) to Koen Paemeleire.

REFERENCES

Ala-Hurula V., Myllyla V., Hokkanen E. Ergotamine abuse : results of ergotamine discontinuation, with special reference to the plasma concentrations. *Cephalalgia*, 1982, **2** (4) : 189-195.

Amato L., Davoli M., Ferri M., Gowing L., Perucci C.A. Effectiveness of interventions on opiate withdrawal treatment : an overview of systematic reviews. *Drug Alcohol Depend.*, 2004, **73** (3) : 219-226.

Bahra A., Walsh M., Menon S., Goadsby P. J. Does chronic daily headache arise de novo in association/with regular use of analgesics ? *Headache*, 2003, **43** (3) : 179-190.

Bigal M.E., Krymchantowski A.V., Rapoport A.M. Prophylactic migraine therapy : emerging treatment options. *Curr. Pain Headache Rep.*, 2004, **8** (3) : 178-184.

Brandes J.L., Marcus D.A. Migraine management during pregnancy. In : *Migraine in women*. Loder E., Marcus D. A. (eds.). Canada, BC Decker Inc., 2004, 112-121.

Catarci T., Fiacco F., Argentino C., Sette G., Cerbo R. Ergotamine-induced headache can be sustained by sumatriptan daily intake. *Cephalalgia*, 1994, **14** (5) : 374-375.

Colas R., Munoz P., Temprano R., Gomez C., Pascual J. Chronic daily headache with analgesic overuse : epidemiology and impact on quality of life. *Neurology*, 2004, **62** (8) : 1338-1342.

DALESSIO D. J. Clonidine in chronic headaches. *Headache*, 1991, **31** (4) : 257.

DE MARINIS M., JANIRI L., AGNOLI A. Headache in the use and withdrawal of opiates and other associated substances of abuse. *Headache*, 1991, **31** (3) : 159-163.

DIENER H. C., LIMMROTH V. Medication-overuse headache : a worldwide problem. *Lancet Neurol.*, 2004, **3** (8) : 475-483.

DRUCKER P., TEPPER S. Daily Sumatriptan for Detoxification From Rebound. *Headache*, 1998, **38** (9) : 687-690.

EVANS R. W., YOUNG W. B. Droperidol and other neuroleptics/antiemetics for the management of migraine. *Headache*, 2003, **43** (7) : 811-813.

EVERS S., GRALOW I., BAUER B., SUHR B., BUCHHEISTER A., *et al.* Sumatriptan and ergotamine overuse and drug-induced headache : a clinicoepidemiologic study. *Clin. Neuropharmacol.*, 1999, **22** (4) : 201-206.

FREITAG F. G., LAKE A. 3rd, LIPTON R., CADY R., DIAMOND S. *et al.* Inpatient treatment of headache : an evidence-based assessment. *Headache*, 2004, **44** (4) : 342-360.

FUH J.-L., WANG S.-J., LU S.-R., JUANG K.-D. Does medication overuse headache represent a behavior of dependence ? *Pain*, 2005, **199** : 49-55.

FUMAL A., LAUREYS S., DI CLEMENTE L., BOLY M., BOHOTIN V. *et al*. Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine. *Brain*, 2006, **129** : 543-550.

GRAZZI L., ANDRASIK F., D'AMICO D., LEONE M., USAI S. *et al.* Behavioral and pharmacologic treatment of transformed migraine with analgesic overuse : outcome at 3 years. *Headache*, 2002, **42** (6) : 483-490.

HAND P. J., STARK R. J. Intravenous lignocaine infusions for severe chronic daily headache. *Med. J. Aust.*, 2000, **172** (4) : 157-159.

HEADACHE CLASSIFICATION COMMITTEE OF THE INTERNATIONAL HEADACHE SOCIETY. The International Classification of Headache Disorders : 2nd edition. *Cephalalgia*, 2004, **24 Suppl 1** : 9-160.

HERING R., STEINER T. J. Abrupt outpatient withdrawal of medication in analgesic-abusing migraineurs. *Lancet*, 1991, **337** (8755) : 1442-1443.

KATSARAVA Z., FRITSCHE G., MUESSIG M., DIENER H. C., LIMMROTH V. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology*, 2001, **57** (9) : 1694-1698.

KATSARAVA Z., DIENER H. C., LIMMROTH V. Medication overuse headache : a focus on analgesics, ergot alkaloids and triptans. *Drug Saf.*, 2001, **24** (12) : 921-927.

KAUBE H., MAY A., PFAFFENRATH V. Sumatriptan. *BMJ*, 1994, **308** (6943) : 1573-1574.

KAUBE H., HOSKIN K. L., GOADSBY P. J. Lignocaine and headache : an electrophysiological study in the cat with supporting clinical observations in man. *J. Neurol.*, 1994, **241** (7) : 415-420.

KOSEOGLU E., AKBOYRAZ A., SOYUER A., ERSOY A. O. Aerobic exercise and plasma beta endorphin levels in patients with migrainous headache without aura. *Cephalalgia*, 2003, **23** (10) :972-976.

KRYMCHANTOWSKI A. V., BARBOSA J. S. Prednisone as initial treatment of analgesic-induced daily headache. *Cephalalgia*, 2000, **20** (2) : 107-113.

KRYMCHANTOWSKI A. V. Overuse of symptomatic medications among chronic (transformed) migraine patients : profile of drug consumption. *Arq. Neuropsiquiatr.*, 2003, **61** (1) : 43-47.

KRYMCHANTOWSKI A. V., MOREIRA P. F. Out-patient detoxification in chronic migraine : comparison of strategies. *Cephalalgia*, 2003, **23** (10) : 982-993.

LANTÉRI-MINET M., AURAY J.-P., EL HASNAOUI A., DARTIGUES J. F., DURU G. *et al.* Prevalence and description of chronic daily headache in the population in France. *Pain*, 2003, **102** : 143-149.

LENARDUZZI P., SCHOENEN J., SIANARD-GAINKO J. Efficacy of clomipramine during the weaning period in drug abuse headaches : a blinded study. *New Trends in Clin. Neuropharm.*, 1988, **II** (2) : 162.

LIMMROTH V., KATSARAVA Z., FRITSCHE G., PRZYWARA S., DIENER H. C. Features of medication overuse headache following overuse of different acute headache drugs. *Neurology*, 2002, **59** (7) : 1011-1014.

LINTON-DAHLOF P., LINDE M., DAHLOF C. Withdrawal therapy improves chronic daily headache associated with long-term misuse of headache medication : a retrospective study. *Cephalalgia*, 2000, **20** (7) : 658-62.

LODER E., BIONDI D. Oral phenobarbital loading : a safe and effective method of withdrawing patients with headache from butalbital compounds. *Headache*, 2003, **43** (8) : 904-909.

LODER E. Migraine diagnosis and treatment. *Prim. Care*, 2004, **31** (2) : 277-292.

MATHEW N. T. Amelioration of ergotamine withdrawal symptoms with naproxen. *Headache*, 1987, **27** (3) : 130-133.

MATHEW N. T., KURMAN R., PEREZ F. Drug induced refractory headache – clinical features and management. *Headache*, 1990, **30** (10) : 634-638.

PAEMELEIRE K., BAHRA A., EVERS S., MATHARU M. S. 1, GOADSBY P. J. Medication-overuse headache : under-recognized in cluster headache patients. *Acta Neurol. Belg. Supp.*, 2004 **104** : 77.

PAGELER L. *et al.* Prednisone in the treatment of medication withdrawal headache following medication overuse headache : a placebo-controlled, double-blind and randomized pilot study. *Cephalalgia*, 2004, **24** : 792.

PASCUAL J., COLAS R., CASTILLO J. Epidemiology of chronic daily headache. Curr. Pain Headache Rep., 2001, **5** (6) : 529-536.

PINI L. A., BIGARELLI M., VITALE G., STERNIERI E. Headaches associated with chronic use of analgesics : a therapeutic approach. *Headache*, 1996, **36** (7) : 433-439.

QUALITY STANDARDS SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY. Practice parameter : appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus (summary statement). *Neurology*, 1995, **45** (3 Pt 1) : 585-587.

RADAT F., SAKH D., LUTZ G., EL AMRANI M., FERRERI M., *et al*. Psychiatric comorbidity is related to headache induced by chronic substance use in migraineurs. *Headache*, 1999, **39** (7) : 477-480.

RASKIN N. H. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. *Neurology*, 1986, **36** (7) : 995-997.

ROBBINS L., REMMES A. Outpatient repetitive intravenous dihydroergotamine. *Headache*, 1992, **32** (9) : 455-458.

SAPER J. R., HAMEL R. L., LAKE A. E. Medication overuse headache (MOH) is a biobehavioral disorder. *Cephalalgia*, 2005, **25** : 545-546.

SCHER A. I, STEWART W. F., LIBERMAN J., LIPTON R. B. Prevalence of Frequent Headache in a Population Sample. *Headache*, 1998, **38** (7) : 497-506.

SCHNIDER P., AULL S., FEUCHT M., MRAZ M., TRAVNICZEK A., *et al.* Use and abuse of analgesics in tension-type headache. *Cephalalgia*, 1994, **14** (2) : 162-167.

SCHWARTZ T. H., KARPITSKIY V. V., SOHN R. S. Intravenous valproate sodium in the treatment of daily headache. *Headache*, 2002, **42** (6) : 519-522.

SILBERSTEIN S. D., SCHULMAN E. A., HOPKINS M. M. Repetitive intravenous DHE in the treatment of refractory headache. *Headache*, 1990, **30** (6) : 334-339.

SILBERSTEIN S. D., LIPTON R. B. Chronic daily headache, including transformed migraine, chronic tension type headache, and medication overuse. In : *Wolff's headache and other head pain*. SILBERSTEIN S. D., LIPTON R. B., DALESSIO D. J. (ed.). New York, Oxford University Press, 2001, 247-282.

SILBERSTEIN S. D., GOADSBY P. J. Migraine : preventative treatment. *Cephalalgia*, 2002, **22** (7) : 491-512.

SMITH T. R. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache*, 2002, **42** (3) : 175-177.

SULLIVAN J. T., SELLERS E. M. Treatment of the barbiturate abstinence syndrome. *Med. J. Aust.*, 1986, **145** (9) : 456-458.

VASCONCELLOS E., PINA-GARZA J. E., MILLAN E. J., WARNER J. S. Analgesic rebound headache in children and adolescents. *J. Child Neurol.*, 1998, **13** (9) : 443-447.

VON KORFF M., GALER B. S., STANG P. Chronic use of symptomatic headache medications. *Pain*, 1995, **62** (2) : 179-186.

WARNER J. S. Time required for improvement of an analgesic rebound headache. *Headache*, 1998, **38** (3) : 229-230.

WARNER J. S. The outcome of treating patients with suspected rebound headache. *Headache*, 2001, **41** (7) : 685-692.

WILLIAMS D. R., STARK R. J. Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. *Cephalalgia*, 2003, **23** (10) : 963-971.

YOUNG W. B. Medication Overuse Headache. *Curr. Treat. Options Neurol.*, 2001, **3** (2) : 181-188.

ZED P. J., LOEWEN P. S., ROBINSON G. Medication-induced headache : overview and systematic review of therapeutic approaches. *Ann. Pharmacother.*, 1999, **33** (1) : 61-72.

ZIEGLER D. K. Opiate and opioid use in patients with refractory headache. *Cephalalgia*, 1994, **14** (1) : 5-10.

ZWART J. A., DYB G., HAGEN K., SVEBAK S., HOLMEN J. Analgesic use : a predictor of chronic pain and medication overuse headache : the Head-HUNT Study. *Neurology*, 2003, **61** (2) : 160-164.

Prof. Dr. K. PAEMELEIRE,
Department of Neurology 1K12,
Ghent University Hospital,
De Pintelaan 185,
B-9000 Ghent (Belgium).
E-mail : Koen.Paemeleire@Ugent.be