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Preliminary results of a withdrawal and detoxification therapeutic regimen in patients with probable chronic migraine and probable medication overuse headache

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Abstract Chronic migraine (CM) is an invalidating condition affecting a significant population of headache sufferers, frequently associated with medication overuse headache (MOH). Controlled trials and guidelines for the treatment of MOH are currently not available. We studied the efficacy of a therapeutic regimen for the withdrawal of the overused drug and detoxification in a sample of patients suffering from probable CM and probable MOH during admission in eight hospitals of Piemonte-Liguria-Valle d'Aosta. Fifty patients, 42 females (84%) and 8 males (16%), mean age at observation 50.66 ± 13.08 years, affected by probable CM and daily medication overuse following IHS diagnostic criteria were treated as inpatients or in a day hospital. Headache index (HI) and daily drug intake (DDI) were used for evaluating the severity of headache and medication overuse. The patients were treated by abrupt discontinuation of the overused drug and by a therapeutic protocol including i.v. hydration, dexamethasone, metoclopramide and benzodiazepines for 7–10 days. Prophylactic medication was started immediately after admission. Analgesics or triptans were used under medical control only in cases of severe rebound headache. Diagnostic protocol

included routine blood tests (at admission and at discharge), dosage of B12 and folic acid. Patients underwent follow-up controls one, three and six months after discharge. The initial diagnosis was probable CM in almost all patients included in the study (41 patients); in nine patients the diagnosis was not specified (coded only as CDH). The overused medications were simple analgesics in 17 cases (34%), combination analgesics in 19 cases (38%), triptans alone or with analgesics in 13 cases (26%) and ergotamine in 2 cases (4%). We collected data from 39 patients at first follow-up (1 month), 32 after 3 months and 14 after 6 months. Mean HI was 0.91 at admission, 0.22 at discharge, 0.38 after 30 days, 0.46 after 3 months and 0.48 after 6 months. Mean DDI was 2.80 at admission, 0.39 at discharge, 0.41 after 1 month, 0.52 after 3 months and 0.59 after 6 months. These results are on average positive and tend to remain stable with time. Although preliminary and obtained on a limited number of patients at 6-month follow-up, our results seem to be encouraging about the use of the proposed therapeutic protocol.

Key words Chronic daily headache • Chronic migraine • Medication overuse • Detoxification

Introduction

Chronic daily headache (CDH) is one of the main therapeutic problems within primary headaches. Chronic migraine (CM) (following ICHD-II: 1.5.1 [1]), is one of the most frequent causes of CDH.

Chronic abuse of ergotamine [2], analgesics [3], opioids [4] and triptans [2–5] may lead to medication-overuse headache (MOH), a secondary headache frequently associated with CDH. Abrupt withdrawal of ergotamine, analgesics and triptans [6] can also cause rebound headache. The treatment of CDH and MOH includes the withdrawal of the abused drug [7]. Further, some therapeutic protocols were proposed [8, 9] but controlled trials and guidelines are currently not available. Hospitalisation is recommended by several authors [10], but without general consent [11].

We studied the efficacy of a withdrawal and detoxification therapeutic regimen in 50 patients suffering from probable CM and probable MOH, performed within eight hospital headache centres. This protocol was followed by a six-month follow-up.

Materials and methods

Fifty patients, 42 females (84%) and eight males (16%), mean age at observation 50.66±13.08 years (range 24–76), affected by probable CM (ICHD-II 1.6.5) and probable MOH (ICHD-II 8.2.7) underwent a withdrawal and detoxification therapeutic regimen as inpatients (25, 50%) or in a day hospital (25, 50%).

Inclusion criteria were:

1. age ≥18 years;
2. diagnosis of CDH;
3. headache index (HI) ≥0.7;
4. daily drug intake (DDI) ≥1;
5. the above conditions having lasted for at least 6 months;
6. verbal informed consent.

The patients were enrolled after a clinical neurological evaluation by an experienced headache specialist including diagnosis and time patterns of primary headache, comorbidity, abused drug, previous prophylaxes and neurological examination. HI and DDI were

used for evaluating the severity of headache and medication overuse within a one-month run-in period (T0). These data were collected mostly as anamnestic data; some of the patients filled out a headache diary. Clinical characteristics of the population are shown in Table 1.

At admission (as inpatients or in a day hospital, according to severity of the headache, amount and type of abused drug, and preference of the patient), they underwent a diagnostic protocol including blood tests (at admission and at discharge), dosage of B12 and folic acid.

The treatment included:

1. Immediate withdrawal of all abused drugs;
2. i.v. hydration (1000–1500 cc of saline solution);
3. i.v. anxiolytic therapy (i.e., clordemetildiazepam 1–3 mg daily or diazepam 5–15 mg daily);
4. i.v. dexamethasone (8 mg daily);
5. i.v. metoclopramide (10 mg daily).

In case of severe headache attacks, only single drugs were allowed (triptans, 1 cp. daily; or lysine acetylsalicylate, 1000 mg daily), and always different from the abused drug. Eight patients (16%) took butalbital-containing preparations (mean daily dose 306.25 mg), but none of them presented symptoms of dependence with need of phenobarbital therapy. Duration of treatment could vary from nine to fifteen days. Prophylaxis was continued if present at the beginning of treatment; if not, it was immediately started. All patients were instructed about the positive effects of behavioural modifications. Follow-up data were collected by means of a headache diary.

Patients were evaluated before (T0) and after (T10) our therapeutic regimen. They underwent follow-up controls one (T30), three (T90) and six months (T120) after discharge. Due to the limited number of patients seen at the six-month follow-up visit, we restricted the evaluation of results to the 32 patients seen at the three-month follow-up visit. Statistical evaluation was performed on HI and DDI using Student's *t*-test vs. T0 data.

Results

The initial diagnosis was probable chronic migraine (1.6.5) in 41/50 patients; in 9 patients the diagnosis was only coded as CDH. The overused medications were simple analgesics/NSAIDs in 14 cases (28%), analgesics/NSAIDs in combination in 22 cases (44%), triptans alone in 6 cases

Table 1 Patients' characteristics at observation. Data are expressed as mean±SD (range) except otherwise indicated

	In-patients	Day hospital	Total
Males, <i>n</i>	3	5	8
Females, <i>n</i>	22	20	42
Mean age at observation, years	49.12±12.85 (24–74)	52.20±13.39 (29–76)	50.66±13.08 (24–76)
Length of overuse, years	4.41±8.10 (6 m–30 y)	1.80±3.53 (6 m–15 y)	3.41±6.27 (6 m–30 y)
Headache index	0.94±0.11 (0.7–1)	0.89±0.14 (0.7–1)	0.91±0.13 (0.7–1)
Daily drug intake	3.12±2.07 (1–10)	2.48±1.39 (1–6)	2.80±1.77 (1–10)

(12%) or in association with analgesics/NSAIDs in 6 cases (12%) and ergot derivatives (in combination) in 2 cases (4%). Nineteen (38%) of our patients took more than one preparation. Twenty-three patients (46%) took caffeine-containing preparations (mean daily dose 270 mg). None of our patients took opioid-containing preparations.

Comorbidity included anxious depression in 24 patients (48%), arterial hypertension in 8 patients (16%) and obesity in 3 patients (6%). Only in one case gastric disorders were reported.

Previous prophylactic treatments were: tricyclic antidepressants in 18 cases; calcium antagonists in 15 cases; beta-blockers in 12 cases; SSRI in 8 cases; antiepileptic agents in 8 cases; pizotifen in 4 cases; other pharmacological prophylaxes in 5 cases; and non-pharmacological treatments in 2 cases (in 20 cases multiple prophylactic treatments were reported). Seventeen patients did not take any prophylaxis.

We found altered values of blood tests at the first visit only in a minority of patients: high cholesterol levels in 7 cases, alteration of hepatic enzymes in 2 cases, low folate values in 2 cases and mild hyperglycaemia in 1 case.

Three patients were early drop-outs and six were lost at follow-up. Preliminary data were collected from 39 patients after 1 month, 32 after 3 months and 14 after 6 months.

The suggested prophylaxis was: sodium valproate in 27 cases, amitriptyline in 6 cases, flunarizine in 6 cases, propranolol in 6 cases, SSRI in 5 cases, topiramate in 5 cases and other prophylaxes in 2 cases. In some cases we suggested a combined prophylaxis.

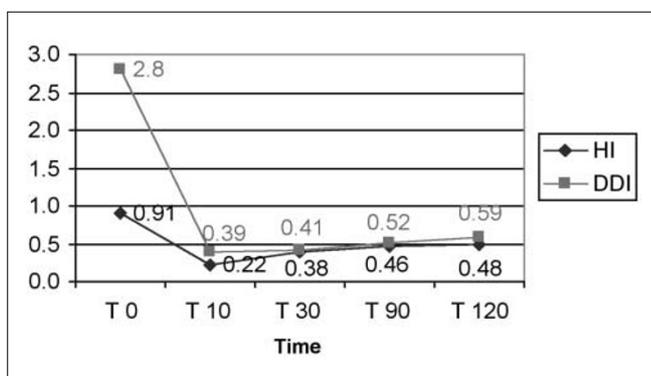


Fig. 1 Time course of HI and DDI

Table 2 Statistical evaluation (Student's *t*-test) on 32 patients at T0, T10, T30, T90

	HI	<i>p</i> vs. T0	DDI	<i>p</i> vs. T0
T0	0.94±0.11		3.03±1.96	
T10	0.21±0.27	<0.0001	0.36±0.65	<0.0001
T30	0.38±0.34	<0.0001	0.40±0.58	<0.0001
T90	0.46±0.36	<0.0001	0.52±0.60	<0.0001

The time course of HI and DDI are shown in Figure 1. Statistical evaluation of preliminary data is shown in Table 2. However, data from these 32 patients do not substantially differ from those regarding all patients.

At the T30 visit, following the course of headache and medication overuse, we were able to modify the original diagnosis only in 26/32 patients, who withdrew drug overuse. In 23 of them headache significantly improved, allowing a diagnosis of MOH. The diagnosis was refined following the revision of criteria for 8.2 *Medication overuse headache* [12], so 4 were diagnosed as triptan-overuse headache (8.2.2), 3 as *Analgesic-overuse headache* (8.2.3), 9 as *Combination analgesic-overuse headache* (8.2.5), and 7 as *Medication-overuse headache attributed to combination of acute medications* (8.2.6). Three patients reported persistence of frequent migrainous attacks despite prophylaxis and so received a definite diagnosis of CM (ICHD-II 1.5.1). Six out of 32 patients continued medication overuse; their diagnosis remained probable CM and probable MOH.

At T90, 19/32 patients (59.4%) experienced a significant relief from headache (below one half of the initial frequency), 24/32 (75.0%) significantly reduced drug intake, and 8 (25.0%) were therapeutic failures.

Discussion

Although only preliminary, our data are in accordance with previous observations [13] and are encouraging for the use of the protocol. The differences in HI and DDI before and after treatment are highly significant. These results tend to remain stable with time. We obtained also a good rate of positive individual results (59.4% for headache relief and 75.0% for lowering drug intake).

It is difficult, due to the limited number of patients, to draw conclusions from these data. We found only a correlation between duration of overuse and unsuccessful outcome (patients with a successful outcome had overused medications for 1.71 ± 2.27 years; those with unsuccessful outcome had overused for 7 ± 10.65 years: $p < 0.05$). No correlation between type and amount of overused drug and successful outcome was found.

The critical period for a good outcome in these patients is the first six months after detoxification.

We will continue the observation in the long-term following the promising results observed.

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