Abstract Oral contraceptive-induced menstrual migraine (OCMM) is a poorly defined migraine subtype mainly triggered by the cyclic pill suspension. In this pilot, open-label trial we describe its clinical features and evaluate the efficacy of frovatriptan in the treatment of its acute attack. During the first 3 months of the study 20 women (mean age 32.2±7.0, range 22–46) with a 6-month history of pure OCMM recorded, in monthly diary cards, clinical information about their migraine. During the 4th menstrual cycle they treated an OCMM attack with frovatriptan 2.5 mg. The majority of attacks were moderate/severe and lasted 25–72 h or more, in the presence of usual treatment. Generally an OCMM attack appeared within the first 5 days after the pill suspension, but in 15% of cases it started later. After frovatriptan administration, headache intensity progressively decreased (2.4 at onset, 1.6 after 2 h, 1.1 after 4 h and 0.8 after 24 h; \( p=0.0001 \)). In 55% of patients pain relief was reported after 2 h. Ten percent of subjects were pain-free subjects after 2 h, 35% after 4 h and 60% after 24 h (\( p=0.003 \) for trend); 36% relapsed within 24 h. Rescue medication was needed by 35% of patients; 50% of frovatriptan-treated required a second dose. Concomitant nausea and/or vomiting, photophobia and phonophobia decreased significantly after drug intake. OCMM is a severe form of migraine; actually its clinical features are not always exactly identified by the ICHD-II classification. However, treatment with frovatriptan 2.5 mg might be effective in its management.

Keywords Oestrogen withdrawal · Frovatriptan · Menstrual migraine · Oral contraceptives

Introduction Menstrual migraine (MM) appearing in patients that are on oral contraceptives (oral contraceptive-induced menstrual migraine, OCMM) is probably a quite common, albeit poorly defined, MM subtype [1] mainly caused by oestrogen withdrawal occurring during the week of pill suspension. This type of headache, codified by the ICHD-II classification [2] as oestrogen-withdrawal headache (code 8.4.3), is defined as “a headache or migraine that develops within 5 days after cessation of oestrogen use and resolves within 3 days (oestrogen use must have lasted for at least 3 weeks prior to cessation)”. It is probably a severe and disabling form of migraine [3–5], but actually very few studies are tailored to define the clinical profile of this type of headache, particularly in the specific case of pure OCMM. Moreover, double-blind, randomised clinical trials have shown that MM attacks can be successfully treated [6–10] or prevented [11–13] with triptans [14]. Their efficacy in the acute management of OCMM attacks, however, has not been studied in specific trials till now. Frovatriptan is a second-generation triptan whose high selectivity for the cerebral vasculature, long elimination half-life and high persistence of therapeutic action may be useful in preventing MM [15], probably with a better safety profile than other triptans [16].
The present study was carried out in order to define the clinical features of OCMM and to test the efficacy of frovatriptan in the acute treatment of an OCMM attack.

**Patients and methods**

This pilot, open-label, uncontrolled study included 34 women aged 18 years or older; all of them had been taking monophasic combined oral contraceptives (21 days on/7 days off regimen) for at least 12 months and had a documented history of pure OCMM. The women selected attended our Women’s Headache Center and were chosen after a careful review of their diary cards, as all patients are usually requested to regularly complete daily diary cards as part of their routine management.

The inclusion criteria were: (1) a 6-month history of pure OCMM, with attacks appearing exclusively in the pill-free week of the menstrual cycle, irrespective of the day of onset of bleeding; (2) all frovatriptan-naïve patients.

The exclusion criteria were contraindications to the use of triptans (ischaemic heart disease, multiple risk factors for coronary artery disease, cerebrovascular or other cardiovascular diseases, severe arrhythmias or conduction disturbances, uncontrolled hypertension, or history of basilar or hemiplegic migraine), severe hepatic or renal insufficiency or other clinically relevant diseases, as well as pregnancy and breast-feeding.

Our study had a length of 4 menstrual cycles and its aim was to observe the clinical features of OCMM during 3 consecutive menstrual cycles, in the presence of usual symptomatic treatment, and to test the efficacy of frovatriptan in the following menstrual cycle.

In order to achieve a correct diagnosis, we included in the study only patients showing pure OCMM in all 3 menstrual cycles taken into consideration.

After a thorough anamnestic investigation on the clinical features of their migraine, women were provided with 3 monthly diary cards. All patients were required to fill in the diaries for a period of 3 menstrual cycles (period A), recording the following information for each migraine attack as it occurred: date of onset; presence/absence of aura symptoms; quality and side of pain; peak intensity (0=no headache, 1=mild headache, 2=moderate headache and 3=severe headache); occurrence of nausea, vomiting, photophobia and phonophobia; and duration of attack in the presence of usual treatment. In the same diary patients recorded the days of pill suspension and those of menstrual bleeding.

After this observation period, patients entered the second part of the study (period B), in which they were instructed to take a single dose of frovatriptan 2.5 mg per os at the onset of a moderate or severe OCMM attack. A second dose could be taken if symptoms were alleviated but recurred within 24 h, with a 2-h lapse time between each dose. Alternatively, patients with moderate or severe headache after 2 h were allowed to take optional rescue medication in the form of standard analgesics (other than triptans or ergot derivatives).

During period B patients continued to record information about migraine attacks in the same diary used during period A. In addition, they recorded in a specific treatment card the following information about the attack treated with study medication: headache intensity at onset and at 2, 4 and 24 h after drug administration, according to the four-point anchored scale; occurrence of nausea, vomiting, photophobia and phonophobia at the same time; use of a second dose of frovatriptan or of a rescue medication.

Data analysis

We analysed the diary cards collected in period A and focused on two main aspects: the duration of OCMM attacks and the temporal window of the onset of the attack, as these are the main parameters which define the oestrogen-withdrawal headache in the ICHD-II classification.

As far as the treatment was concerned, we evaluated the following: (a) the percentage of patients with pain relief, defined as reduction of headache from moderate or severe at onset, to mild or none, (b) the percentage of patients who were pain-free, (c) the percentage of patients without associated symptoms, (d) the percentage of patients who used rescue medication, and (e) the percentage of those needing a second dose of frovatriptan. Recurrence rate (defined as the return of a severe/moderate headache within 24 h in patients who experienced relief 2 h after dosing) was also calculated. Temporal trends were explored with non-parametric Friedman’s test for repeated measures.

**Results**

Only 20 patients (mean age 32.2±7.0 years, range 22–46) out of 34 enrolled had a positive history for pure OCMM, as documented by diary cards. Ten women out of the 14 excluded were also suffering from headache outside the pill-free week, 2 of them had not correctly filled in the diary cards and 2 of them had not suffered OCMM attacks for 3 months in a row. Final evaluation was therefore based on data obtained from the former 20 patients. All patients presented attacks with the typical features of migraine without aura; in fact, no patient reported aura symptoms. Clinical data are presented in Table 1. All OCMM attacks were of moderate (45%) or severe (55%) intensity. In the majority of patients migraine usually lasted at least 2 days in the presence of usual treatment, but 15% of attacks exceeded the 72-h upper limit proposed for migraine without aura in the IHS Classification (6). Migraine attacks appeared within the first 5 days...