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Frovatriptan vs. transdermal oestrogens or naproxen sodium for the prophylaxis of menstrual migraine

Abstract Acute treatment of menstrual migraine (MM) attacks is often incomplete and unsatisfactory, and perimenstrual prophylaxis with triptans, oestrogen supplementation or naproxen sodium may be needed for decreasing frequency and severity of the attack. In this pilot, open-label, non-randomised, parallel group study we evaluated, in 38 women with a history of MM, the efficacy of frovatriptan (n=14) 2.5 mg per os or transdermal oestrogens (n=10) 25 μg or naproxen sodium (n=14) 500 mg per os once-daily for the short-term prevention of MM. All treatments were administered in the morning for 6 days, beginning 2 days before the expected onset of menstrual headache. All women were asked to fill in a diary card, in the absence of (baseline) and under treatment, in order to score headache severity. All women reported at least one episode of MM at baseline. During treatment all patients taking transdermal oestrogens or naproxen sodium and 13 out of the 14 patients (93%) taking frovatriptan had at least one migraine attack (p=0.424). Daily incidence of migraine was significantly (p=0.045) lower under frovatriptan than under transdermal oestrogens or NS. At baseline, the overall median score of headache severity was 4.6, 4.2 and 4.3 in the group subsequently treated with frovatriptan, transdermal oestrogens and naproxen sodium, respectively (p=0.819). During treatment the median score was significantly lower under frovatriptan (2.5) than under transdermal oestrogens (3.0) and naproxen sodium (3.9, p=0.049). This was evident also for each single day of observation (p=0.016). Among treatments differences were particularly evident for the subgroup of patients with true MM (n=22) and for frovatriptan vs. naproxen sodium. This study suggests that short-term prophylaxis of MM with frovatriptan may be more effective than that based on transdermal oestrogens or naproxen sodium.

Keywords Frovatriptan • Menstrual migraine • Transdermal oestrogens • Naproxen sodium • True menstrual migraine • Menstrually related migraine
**Introduction**

According to recent statistics, migraine affects 15%-20% of women, being more frequent in this population than in men [1,2]. The most common form of migraine in women is menstrual migraine (MM) [3], a migraine without aura occurring regularly in close relationship with the onset of menstruation (between 2 days before and up to 3 days after the onset of bleeding) [4]. There are two acknowledged types of MM: the so-called menstrually related migraine, characterised by attacks occurring also at other times of the cycle, and the pure or true MM, starting exclusively between the days immediately before and immediately after the first day of the menstrual cycle [3,4].

The origin of MM is to be ascribed to the sudden fall of serum oestrogen levels immediately preceding menses, triggering abnormal neurotransmitter and neurohormonal responses or abnormal release of prostaglandins [3-6].

Effective acute therapy is the mainstay of management for menstrual attacks, although there is much evidence that attacks linked to menstruation may not respond to the usual antimigraine medications [7,8]. In this case peri-menstrual prophylaxis with naproxen sodium, oestradiol supplementation or triptans has been shown to be effective in decreasing attack frequency and severity [9-14]. Among the various triptans effectively employed in MM, frovatriptan is a second-generation triptan showing high selectivity for cerebral vasculature, long elimination half-life and high persistence of therapeutic action and may ensure an effective preventive treatment of MM [11,15], with a better safety profile than other triptans [16].

In the present study the efficacy of frovatriptan in the prevention of MM attacks has been compared with that of other treatments (transdermal oestrogens and naproxen sodium) commonly and widely employed for this purpose.

**Methods**

Patients

Female subjects, aged 18 years or more, with at least a 12-month documented history of menstrual headaches occurring from 2 days before to the first 3 days of menstruation in at least two out of three menstrual cycles, as defined by Headache Classification Committee of the International Headache Society [4], were enrolled. Only women with regular menstrual cycles in the previous 6 months [17] and able to predict the onset period of menstrual headache could be enrolled in the study. Exclusion criteria were: (a) occurrence of more than three migraine attacks per month not classified as MM attacks, (b) a history of cardiovascular or cerebrovascular disease, renal or liver insufficiency or other clinically relevant diseases, (c) moderate or severe arterial hypertension or mild uncontrolled arterial hypertension, (d) more than 15 headache days per month, exclusive of migraine headache, (e) known hypersensitivity to frovatriptan, (f) treatment with ergot medications, other 5-HT agonists or MAO inhibitors at the time of enrolment, (g) any change in the type or dose of any prophylactic migraine medication in the 2 months prior to screening or any anticipated change during study participation.

Written informed consent was obtained from all patients prior to their inclusion into the study.

Study design

This was a pilot, open-label, non-randomised, parallel group study. Eligible patients were treated with frovatriptan 2.5 mg per os or transdermal oestrogen 25 μg or naproxen sodium 500 mg per os once-daily. All treatments were administered in the morning for 6 days, beginning 2 days before the expected onset of the menstrual headache (considering day 0 as when bleeding started). Assessment of efficacy was based on a patient’s diary card where intensity of migraine had to be reported on a daily basis. The diary had to be completed by patients on two occasions: the first in the absence of treatment (control or baseline) and the second during treatment with one of the three drugs. Headache severity was rated using a 10-point anchored scale where 0 is no headache and 10 is severe headache. No escape or rescue medication was allowed during the study.

Data analysis

As this was a pilot study, no formal sample size estimation was carried out at the time of study planning. Drug efficacy was assessed by calculating the percentage of patients with MM (incidence of the disease) and the score of headache intensity or severity from 2 days before to 3 days after menses. Study variables were also computed by day of treatment, separately for the baseline and treatment period. Analysis for subgroups of patients with true MM and menstrually related migraine was also performed.

Incidence of MM was compared among treatments by the non-parametric Kruskal–Wallis test. Given the non-normal distribution of headache severity score, as verified by the Shapiro–Wilk test, the score was summarised using median values and among-treatments comparison was done by the non-parametric Kruskal–Wallis test. An analysis of variance for repeated measures corrected for multiple comparisons was used for confirmatory analysis. A p<0.05 was taken as the minimum level of statistical significance.
Results

Demographic and clinical data at entry

A total of 38 patients were enrolled, of whom 14 (37%) treated with frovatriptan, 10 (26%) with transdermal oestrogens and 14 (37%) with naproxen sodium. All patients had a previous diagnosis of MM, the most common form being true MM (58% of patients). Most women had a positive family history for migraine (53%) and were previously taking antimigraine drugs (55%). At baseline, distribution of all demographic and clinical data was not significantly different among the three treatment groups, though some differences were observed in the prevalence of subtypes of MM and in the use of drugs (Table 1).

Incidence of menstrual migraine

In the absence of treatment (baseline) all patients had at least one MM attack. Typically, incidence of migraine attacks was low before menses and rapidly increased after menstruation (Fig. 1). No statistically significant difference (p=0.823) was observed in the incidence of migraine at baseline among the three study treatment groups.

During treatment all patients taking transdermal oestrogens or naproxen sodium and 13 out of the 14 patients (93%) taking frovatriptan had at least one migraine attack (p=0.424 among treatments). Incidence of migraine during each day of observation was significantly (p=0.045) lower under frovatriptan than under transdermal oestrogens or naproxen sodium (Fig. 1), this being particularly true for the subgroup of patients with true MM (average prevalence 60% under frovatriptan, 79% under oestrogens and 78% under naproxen sodium).

![Fig. 1 Percentage (%) of patients with MM at baseline (panel A) and during treatment (panel B), in the group assigned to treatment with frovatriptan 2.5 mg od (open bars, n=14), transdermal oestrogen 25 μg (striped bars, n=10) or naproxen sodium 500 mg od (full bars, n=14). Data are shown for the two days preceding (–2 and –1) and the 3 days following menses (1, 2 and 3), and for the day when bleeding started (0). p refers to interaction between treatment and time]

Table 1 Demographic and clinical data of study population at inclusion (n=34)

|                          | Frovatriptan (n=14) | Transdermal oestrogens (n=10) | Naproxen sodium (n=14) |
|--------------------------|---------------------|-------------------------------|-----------------------|
| Age (years, mean±SD)     | 32±8                | 29±4                          | 34±8                  |
| Subtypes of MM (n, %)    |                     |                               |                       |
| True MM                  | 8 (57)              | 4 (40)                        | 10 (71)               |
| Menstrually-related migraine | 6 (43)             | 6 (60)                        | 4 (29)                |
| Positive family history for migraine (n, %) | 7 (52)             | 6 (60)                        | 7 (53)                |
| Previous treatments for migraine (n, %) |                     |                               |                       |
| Other triptans           | 4 (29)              | 5 (50)                        | 3 (21)                |
| Prophylaxis with calcium antagonists | 2 (14)            | -                             | -                     |
| Prophylaxis with beta-blockers | 1 (7)             | -                             | -                     |
| Oestroprogestins         | –                   | 4 (40)                        | 2 (14)                |
| Concomitant treatments (n, %) | –                 | 3 (30)                        | 1 (7)*                |

*Lansoprazol; *Antipsoriatic treatment
Severity of menstrual migraine

Median scores of headache severity by type of drug at baseline and during treatment are shown in Figure 2. At baseline, headache severity reached its apex between days 0 and 1 with a non-significantly different trend among the three treatment groups ($p=0.277$), the overall median score being 4.6 in the group subsequently treated with frovatriptan, 4.2 in that treated with transdermal oestrogens and 4.3 in that treated with naproxen sodium ($p=0.819$).

During treatment the median score was significantly lower under frovatriptan than under transdermal oestrogens and naproxen sodium (2.5 vs. 3.0 and 3.9, respectively, $p=0.049$). This was evident also for each single day of observation (Fig. 2, among treatments difference $p=0.016$) and in particular for frovatriptan vs. naproxen sodium.

As shown in Figure 3, the superiority of frovatriptan vs. naproxen sodium, in terms of attenuation of headache severity, was evident only for the subgroup of patients with true MM ($p=0.047$ multiple comparisons test).

**Discussion**

In our study perimenstrual prophylaxis with frovatriptan, transdermal oestrogens and naproxen sodium was carried out in women with known MM, according to an open-label, non-randomised, parallel group design. During one perimenstrual period of observation, frovatriptan proved to be superior to transdermal oestrogens and naproxen sodium in reducing the incidence of migraine attacks and their severity, with respect to a previous wash-out period, particularly in the subgroup of women with true MM.

This is the first evidence of a direct comparison of the efficacy of triptans, oestradiol and non-steroidal anti-inflammatory drugs as a prophylactic measure for MM attacks, showing the superiority of triptans over other drugs usually employed for the prevention of this type of migraine. Previous studies have separately assessed the efficacy of these three classes of drugs for prevention of MM. In a small open-label study involving 20 women, sumatriptan given at 25 mg 3 times per day reduced the incidence of headache by 50% as well as its severity, as compared to baseline [13]. In a larger (59 women) open-label study, naratriptan 1 mg given 2 times per day 2 days before menstruation and for the following 6 days for a total of 3 months decreased the frequen-

![Fig. 2 Median score of headache severity at baseline (panel A) and during treatment (panel B), in the group assigned to treatment with frovatriptan 2.5 mg od (continuous line, n=14), transdermal oestrogen 25 μg (dashed line, n=10) or naproxen sodium 500 mg od (dotted line, n=14). Data are shown for the two days preceding (–2 and –1) and the 3 days following menses (1, 2 and 3), and for the day when bleeding started (0). p refers to interaction between treatment and time](image1)

![Fig. 3 Median score of headache severity during treatment in the patients with true MM treated with frovatriptan 2.5 mg od (continuous line) or naproxen sodium 500 mg od (dotted line). Data are shown for the two days preceding (–2 and –1) and the 3 days following menses (1, 2 and 3), and for the day when bleeding started (0). p refers to interaction between treatment and time](image2)
cy of migraine attacks by nearly two over the course of 3 months as compared to placebo [14]. In a double-blind study 2.5 mg of naratriptan 2 times per day, but not 1 mg, was effective in reducing the incidence of headache [12]. Efficacy of frovatriptan 2.5 mg once or twice daily in the short-term prevention of MM was tested vs. placebo in a double-blind study where treatment was commenced 2 days before anticipated MM, preceded by a loading dose of 5 or 10 mg [11]. In this study women taking frovatriptan 2.5 mg once-daily for 3 perimenstrual periods had an incidence of MM of 52% vs. 67% under placebo, the incidence being 41% under frovatriptan 2.5 mg twice-daily. Significant reductions were also observed in headache severity in the group treated with frovatriptan. In our study, incidence of headache after treatment with frovatriptan was only marginally reduced as compared to the control period, but the headache severity was consistently blunted, significantly more than under naproxen sodium or transdermal oestrogens. This is consistent with results of previous studies based on short-term prevention of MM with such treatments.

Indeed, even though use of oestrogens for prevention of MM has been supported by the hypothesis that this condition may be due to oestrogen withdrawal or fluctuations, stabilised or prevented by oestrogen supplementation, use of oestradiol patch at doses even higher than those used in our study (50 vs. 25 μg of our study) did not affect the incidence, duration and severity of migraine attacks compared with placebo [18]. In a double-blind, placebo-controlled study, short-term preventive treatment with naproxen sodium, at doses higher than those used in our study (550 mg twice daily vs. 500 mg once-daily in our study) reduced the incidence of headache attacks by 33%, with a lesser headache intensity and duration in patients receiving this drug as compared to placebo [19]. In our study neither transdermal oestrogens nor naproxen sodium altered the incidence of headache as compared to the control period. They reduced the severity of headache but in a way consistently and significantly less than frovatriptan.

Unfortunately, as mentioned above, the drug doses used in our study were roughly half of those usually employed in clinical trials assessing the efficacy of preventive treatment of MM and thus the study results might have been underestimated. As a matter of fact it has been demonstrated that patches containing 25 μg (the dose employed in our study) or 50 μg of oestrogens may be poorly effective [20-22], while this is not the case for doses of 100 μg [20], probably because low doses of oestrogens do not allow the critical threshold for their efficacy to be achieved [23]. Besides, use of high-dose oestrogen supplementation may be dangerous, increasing the risk of ischaemic stroke in high-risk women [3]. Regarding naproxen, there are no studies evaluating its efficacy in MM and we must acknowledge that a single 500-mg daily dose may not be optimal for this indication. Also frovatriptan was used at a suboptimal dose, as 5 mg/day is usually considered the minimal effective dose [11], with some efficacy being sometimes observed also at 2.5 mg/day. This administration time scheduling and dosing was chosen because we decided to follow the scheme usually applied by doctors to their patients in our country, though we acknowledge it is far from ideal and optimal.

Another limitation of our study is the limited sample size, and the open-label, non-randomised, pilot study nature of the design. The study was also based on only one perimenstrual period of observation under active drug treatment. However, this is the first study comparing these three treatments in women with MM. As this condition is often more severe than other types of migraine and its response to acute treatment is often less favourable than for other forms of migraine [7-10], our study results strengthen the usefulness of short-term prevention of this condition with triptans, previously reported by open-label and double-blind controlled studies [11-14]. The relatively similar effect of frovatriptan and transdermal oestrogens on severity of headache attacks in the subgroup of women with true MM, and the hypothesised possible interaction between serotonin synthesis and oestrogen [24] in the genesis of MM, also suggests a potential benefit in the combination of these two drugs for prophylaxis of this subtype of MM.

In conclusion, results of our study suggest that short-term prophylaxis of MM with frovatriptan 2.5 mg/day given in the perimenstrual period is more effective than that based on transdermal oestrogens or naproxen sodium in terms of attenuation of headache severity, but not in the reduction of incidence of migraine attacks. Further large double-blind, randomised, placebo-controlled studies are needed to definitively prove the efficacy of frovatriptan vs. other standard prophylactic treatment in this subpopulation of migrainous patients.

References

1. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF (2007) AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 68:343–349
2. Breslau N, Rasmussen BK (2001) The impact of migraine: Epidemiology, risk factors, and co-morbidities. Neurology 56[6 Suppl 1]:4–12
3. Brandes JL (2006) The influence of estrogen on migraine: a systematic review. JAMA 295:1824–1830
4. Headache Classification Committee of the International Headache Society (2004) The International Classification of Headache Disorders. Cephalalgia 24[Suppl 1]:1–160
5. Granella F, Sances G, Allais G, Nappi RE, Tirelli A, Benedetto C et al (2004) Characteristics of menstrual and non-menstrual attacks in women with men- strually related migraine referred to headache centres. Cephalalgia 24:707–716
6. Allais G, Benedetto C (2004) Update on menstrual migraine: from clinical aspects to therapeutical strategies. Neurol Sci 25(Suppl 3):229–231
7. Mannix LK (2003) Management of menstrual migraine. Neurologist 9:207–213
8. Ashkenazi A, Silberstein SD (2006) Hormone-related headache: pathophysiology and treatment. CNS Drugs 20:125–141
9. MacGregor A (2000) Migraine associated with menstruation. Func Neurol 15(Suppl 3):143–153
10. Martin V (2007) Targeted treatment strategies for menstrual migraine. J Fam Pract 56:13–22
11. Silberstein SD, Elkind AH, Schreiber C, Keywood C (2004) A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology 63:261–269
12. Newman L, Mannix LK, Landy S, Silberstein S, Lipton RB, Putnam DG et al (2001) Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. Headache 41:248–256
13. Newman LC, Lipton RB, Lay CL, Solomon S (1998) A pilot study of oral sumatriptan as intermittent prophylaxis of menstruation-related migraine. Neurology 51:307–309
14. Moschiano F, Allais G, Grazzi L, Usai S, Benedetto C, D’Amico D et al (2005) Naratriptan in the short-term prophylaxis of pure menstrual migraine. Neurol Sci 26(Suppl 2):162–166
15. Allais G, Bussone G, De Lorenzo C, Mana O, Benedetto C (2005) Advanced strategies of short-term prophylaxis in menstrual migraine: state of the art and prospects. Neurol Sci 26(Suppl 2):125–129
16. Geraud G, Spierings EL, Keywood C (2002) Tolerability and safety of frova-triptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. Headache 42 [Suppl 2]:93–99
17. Belsey EM, Farley TM (1988) The analysis of menstrual bleeding patterns: a review. Contraception 38:129–156
18. Smits MG, van der Meer YG, Pfeil JP, Rijnierse JJ, Vos AJ (1994) Perimenstrual migraine: effect of Estraderm TTS and the value of contingent negative variation and exteroceptive temporalis muscle suppression test. Headache 34:103–106
19. Sances G, Martignoni E, Fioroni L, Blandini F, Facchinetti F, Nappi G (1990) Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. Headache 30:705–709
20. Pradalier A, Vincent D, Beaulieu P, Baudesson G, Launay J (1994) Correlation between oestradiol plasma level and therapeutic effect on menstrual migraine. In: Rose C, ed. New Advances in Headache Research: 4. London: Smith-Gordon 129–132
21. Paffrenrath VL (1993) Efficacy and safety of percutaneous estradiol vs. placebo in menstrual migraine. Cephalalgia 13[suppl]:244–247
22. Smits MG, van der Meer YG, Pfeil JP, Rijnierse JJ, Vos AJ (1994) Perimenstrual migraine: effect of Estraderm TTS and the value of contingent negative variation and exteroceptive temporalis muscle suppression test. Headache 34:103–106
23. MacGregor EA (2004) Oestrogen and attacks of migraine with and without aura. Lancet Neurol 3:354–361
24. Nappi RE, Sances G, Brundu B, De Taddei S, Sommacal A, Ghiotto N et al (2005) Estradiol supplementation modulates neuroendocrine response to M-chlorophenylpiperazine in menstrual status migraineous triggered by oral contraception-free interval. Hum Reprod 20:3423–3428
