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Managing migraine headaches experienced by patients who self-report with menstrually related migraine: a prospective, placebo-controlled study with oral sumatriptan

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Abstract The objective was to evaluate the efficacy and tolerability of oral sumatriptan (100 mg) in patients who self-reported with menstrually related migraine. A prospective, multicentre, randomised, double-blind, placebo-controlled, two-group crossover study was carried out in 20 UK primary and secondary care surgeries. Of 115 patients with a self-reported history of menstrually related migraine that entered the study, 93 patients completed it. Patients treated all migraine attacks for 2 months with sumatriptan (100 mg) and for 2 months with placebo. The primary endpoint was the proportion of patients reporting headache relief at 4 hours for the first treated attack. Only 11% of patients fulfilled the protocol definition of menstrually related migraine. Patients reported a variable pattern of migraine attacks occurring inside and outside the menstrual window. For the first attack, significantly more patients receiving sumatriptan than placebo reported headache relief for attacks occurring inside (67% *vs.* 33%, p=0.007) and outside (79% *vs.* 31%, p<0.001) the menstrual period. Sumatriptan was generally well tolerated. Oral sumatriptan (100 mg) is an effective and well tolerated acute treatment for patients who report menstrually related migraine.

Key words Headache spectrum • Menstrual migraine • Sumatriptan

Introduction

Migraine is equally common in both genders until puberty, when it becomes approximately three times more prevalent in women than in men [1, 2]. This greater prevalence in women is due, in part, to the influence of female sexual hormones. More than 50% of women relate a periodicity of their migraine attacks to their menstrual cycles [3, 4], although in most cases they also have migraine attacks outside the menstrual period. It has been proposed that menstrual migraine is due to oestrogen withdrawal in the late luteal phase of the normal menstrual cycle acting as a migraine trigger in predisposed individuals [5], but other factors such as prostaglandin release have also been implicated [6]. However, the true prevalence of menstrual migraine attacks (those occurring during the peri-menstrual period) is unclear due to retrospective reports and variable definitions of menstrual migraine [7].

Menstrual migraine attacks are treated with standard acute therapies and with specific prophylactic treatments such as oestrogen supplements taken during the peri-menstrual period [6]. It has been widely considered that menstrual migraine attacks are more severe and less responsive to drug treatments and non-pharmacological approaches than non-menstrual attacks [6, 8], but the data to support this

proposition are somewhat equivocal. Population- and case-based studies have indicated that attacks of migraine at the time of menstruation are more severe, of longer duration and more resistant to treatment than attacks at other times of the month [9–11]. A small study with sumatriptan indicated that the drug was less effective for attacks occurring during menstruation than for those occurring at other times (56% *vs.* 81% of patients reporting relief of their migraine headache 4 hours after treatment, when treated during and outside the menstrual period, respectively) [12]. On the other hand, a population-based epidemiological study indicated that menstrually associated migraine attacks were slightly more painful, but not more disabling, than attacks occurring at other times in the cycle [13]. Also, a recent study has indicated that migraine attacks occurring outside the menstrual period were more disabling to the sufferer than those occurring during the menstrual period [14].

The triptans are selective 5-hydroxytryptamine 1 (5-$HT_{1B/1D}$) receptor agonists, which have been shown to be effective for the acute treatment of migraine [15]. The subcutaneous formulation of sumatriptan [16, 17] and oral formulations of zolmitriptan [18], rizatriptan [19, 20] and eletriptan [21] were shown to be effective treatments for menstrual migraine attacks. However, these studies generally relied on a retrospective diagnosis of menstrual migraine, and assessed the efficacy of the triptan on migraine attacks occurring only at the time of menstruation. What these studies have not investigated is the distribution of migraine attacks inside and outside the menstrual period for patients reporting with menstrual migraine and the clinical profile of the triptans in the spectrum of migraine attacks experienced by these patients.

This study assessed the efficacy of oral sumatriptan (100 mg) on migraine attacks experienced over four menstrual cycles by a group of patients who self-reported with menstrually related migraine. The relationship between migraine attacks and menstruation was collected prospectively, and the study therefore provided an opportunity to re-examine the clinical relevance of the definitions of menstrually related migraine. This study was prospective in design, unlike many other studies conducted with triptans in menstrual migraine.

Patients and methods

Patients

All patients were women aged between 18 and 50 years who self-reported to the investigator with menstrually related migraine (based on patient recall of having experienced a menstrually related migraine attack in two of their last three menstrual cycles and >80% of their attacks falling within the menstrual window in the previous 6 months). Patients presented with a history of one to four moderate or severe migraine attacks with or without aura per month (in accordance with the International Headache Society [IHS] diagnostic criteria pertaining at the time) [22]. The majority of attacks (at least 80%) were reported to occur during the menstrual window (the 8 days starting 3 days before the onset of menstruation). Prophylactic migraine therapy and hormonal therapy were kept constant for 3 and 6 months, respectively, prior to the study and throughout the study. Patients were excluded from the study if they were pregnant or likely to become pregnant during the study, were lactating, or had hypertension (supine diastolic pressure >95 mmHg), ischaemic heart disease, atherosclerotic disease or other concurrent medical conditions that could affect the study data or for which there was a medical contraindication. Patients were also excluded if they were regularly taking analgesics, anti-emetics or anti-histamines, abused ergotamine or alcohol, or had a hypersensitivity to, intolerance of, or contraindication to the use of sumatriptan.

Methods

Study design

This was a multicentre, randomised, double-blind, placebo-controlled, crossover design study conducted in 20 primary and secondary care (neurology and gynaecology clinics) centres in the United Kingdom. The study (Protocol Number GL-MIG-017) was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, primarily through hospital outpatient clinics. Each centre obtained Local Ethics Committee approval before starting the study and all patients gave their written informed consent to participate.

Treatments

Patients were randomised to one of two treatment groups: Group 1 received oral sumatriptan (100 mg) for two menstrual cycles followed by placebo for two menstrual cycles; Group 2 received placebo followed by sumatriptan (100 mg). Patients treated all their migraine attacks of moderate or severe intensity over the four menstrual periods with study medication. Patients could take up to three sumatriptan 100 mg or placebo tablets in any 24-hour period, if the migraine improved but then returned (headache recurrence), providing a minimum of 4 hours elapsed between the doses. If symptoms were not adequately relieved at 4 hours after the first dose, patients could take rescue medication (excluding commercially available sumatriptan or ergotamine-containing medications; other triptans were not available at the time of the study).

Patients recorded on diary cards details of their migraine attacks before treatment and the subsequent response to study medication. Headache severity was rated on a four-point scale: no pain (Grade 0), mild pain (Grade 1), moderate pain (Grade 2) or severe pain (Grade 3). Patients also completed calendar cards to indicate the days on which their menstruation occurred. Patients visited the clinic each month for assessment of their progress and the recording of adverse events.

Endpoints

The primary study efficacy endpoints were the proportions of patients who reported headache relief (a reduction in headache

severity from severe or moderate [Grade 3/2] to mild or none [Grade 1/0]), complete headache relief [Grade 3/2 to Grade 0], any improvement in headache pain [improvement by at least one grade] and complete improvement of headache pain [Grade 1/2/3 to 0], even though patients treating mild [Grade 1] pain could be considered as protocol violators) at 4 hours after taking the first dose of study medication. At the time of this study, the 2-hour time period had not been established as the optimal timescale to record efficacy in migraine studies. A comparison was made of the efficacy of sumatriptan between the sub-set of attacks that commenced inside and outside the menstrual window. Secondary efficacy endpoints included global assessments of the efficacy of treatment, assessed by the patients at the end of each phase of the study as 'excellent', 'good', 'moderate', 'poor' or 'very poor'. Patients also expressed their preference for the study medication at the end of the study. Tolerability was assessed in terms of adverse events reported following treatment with sumatriptan (100 mg) or placebo.

Statistical analysis

Descriptive statistics were calculated for demographic and migraine history data. Data from the first treated attack in each phase of the study formed the basis of the primary efficacy analysis in the intent-to-treat population, as some patients did not treat more than one attack in each phase. The study was powered to demonstrate a significant difference between sumatriptan and placebo. Using large-scale sample theory, a total of 76 evaluable patients were calculated to provide a 90% probability of a result significant at the 1% level (two-tailed). The response to treatment was analysed as a standard two-phase crossover trial with binary data. Estimates of true treatment success rates were derived using a log-linear model [23]. The exact *p*-value was calculated from Prescott's test. When allowing for the effect of menstrual association, a log-linear model was used to derive the estimates of treatment effect in each stratum, and an exact *p*-value as calculated from Prescott's test, stratified for menstrual association. Consistency of treatment effect across the strata was assessed from the patients with different responses in the two phases, using the Zelen test [24]. All comparisons between the treatments were made only after confirmation that there was no evidence to suggest a treatment-by-phase interaction, i.e., a carryover difference from one crossover phase to the other. Identical methods were used to analyse the patients' global assessments of efficacy. A 5% two-tailed significance level was used throughout the study. Tolerability was recorded as descriptive statistics in terms of the number of adverse events and the number and proportion of patients reporting adverse events.

Results

Patient disposition and demography

A total of 115 patients took part in the study, 110 of whom treated at least one migraine attack. Sixty-one patients were randomised to receive sumatriptan for the first phase and placebo for the second phase (Group 1) and 54 were randomised to placebo followed by sumatriptan (Group 2). Ninety-three patients completed the study and 22 withdrew during the study. Reasons given for withdrawal included patients' request (11 patients), adverse events (8 patients), failure to return (8 patients), violation of inclusion and/or exclusion criteria (4 patients), lack of efficacy (3 patients) and other reasons (4 patients). Many of the patients gave more than one reason for their withdrawal.

Demographic data and baseline characteristics of the study population are shown in Table 1, and were similar for the two groups. For the whole study population, the

Table 1 Patient demography and migraine history: denominator figures, 61 (Group 1) and 54 (Group 2), except where indicated

	Group 1 (*n*=61)	Group 2 (*n*=54)	All patients (*n*=115)
Mean age, years (range)	37 (19–49)	40 (19–50)	38 (19–50)
Race, *n* (%)			
Caucasian	59 (97)	53 (98)	112 (97)
Asian	2 (3)	1 (2)	3 (3)
Migraine history, years (range)	14 (1–40)	16 (1–40)	15 (1–40)
Migraine type, *n* (%)			
With aura	1 (2)	0 (0)	1 (1)
Without aura	25 (41)	33 (61)	58 (50)
With and without aura	35 (57)	21 (39)	56 (49)
Average duration of attacks ≥1 day, *n* (%)	55/58 (95)	52/53 (98)	107/111 (96)
Patients using:			
Acute medications, *n* (%)	42 (69)	46 (85)	88 (77)
Prophylactic medications, *n* (%)	9 (15)	8 (15)	17 (15)
Hormone-base therapy, *n* (%)	10 (16)	14 (26)	24 (21)
Patients reporting usual acute treatment good/excellent, *n* (%)	17/57 (30)	10/52 (19)	27/109 (25)

Table 2 Distribution of patients' migraine attacks inside and outside the menstrual window (8 days commencing 3 days prior to the onset of menstruation) during the study: denominator figure=102 patients

% attacks occurring within the menstrual window	Number of patients (%)	
	Patients fulfilling criteria	Patients not fulfilling criteria
100	6 (6)	96 (94)
≥80	11 (11)	91 (89)
≥50	53 (52)	49 (48)

mean age was 38 years (range 19–50 years) and all but three patients (who were Asian) were Caucasian. Patients had a mean migraine history of 15 years, with 50% suffering only from migraine without aura and 49% from migraine with and without aura. One patient reported only attacks of migraine with aura. Almost all patients (96%) reported a history of migraines of long duration, lasting 'one day' or 'several days', even when treated with their usual migraine medication. Most patients (77%) used acute medications, but relatively few used prophylactic medications (15%) or hormone-based therapy (21%) in the month before the study started. The specific prophylactic medications and hormone therapies were not recorded for the patients. However, only 25% of patients rated their usual acute medication as 'excellent' or 'good' at entry into the study. The patients entering this study self-reported with menstrually related migraine (defined in the study protocol as ≥80% of migraine attacks occurring during the menstrual window in the previous 6 months).

Distribution of attacks inside and outside the menstrual window

The median of the mean number of attacks suffered by patients during the study was 2.5 per month. During the study, patients recorded when migraine attacks and menstruation occurred. This information was used to categorise attacks as either inside or outside the menstrual window. This prospective data was used to check the reporting of menstrually related migraine given by each patient at the study outset. Thirteen patients could not be classified, leaving 102 patients to be analysed. When the patients' migraine attacks were compared with their menstrual cycles during the study, only 6% of the patients fulfilled the criteria for pure menstrual migraine (100% of attacks in the menstrual window) and 11% met the study criteria for menstrually related migraine (≥80% of attacks within the menstrual window). Fifty-two per cent of patients had ≥50% of their migraine attacks within the menstrual window (Table 2). No noteworthy pattern was seen in the distribution of the attacks that occurred outside the menstrual window.

Efficacy

Owing to the small number of patients with pure menstrual migraine and protocol-defined menstrually related migraine, efficacy analyses were conducted for the whole study sample. The efficacy of sumatriptan (100 mg) compared with placebo was analysed for the first migraine attack treated for patients who completed both phases of the study. These efficacy analyses were also conducted on patients who treated at least one migraine attack occurring inside or outside the menstrual window in each treatment phase. Significantly more patients receiving sumatriptan (100 mg) than placebo reported headache relief, complete headache relief, headache improvement by at least one grade and complete headache improvement at 4 hours after treatment for migraine attacks occurring both inside and outside the menstrual window (Table 3). Results were similar for attacks occurring inside and outside the menstrual window for all analyses, although relief rates were slightly higher for attacks taking place outside the menstrual period. For all the attacks treated with sumatriptan, headache relief was reported at 4 hours for 80% of attacks occurring outside the menstrual window and 76% of attacks occurring inside the menstrual window.

Patients assessed the efficacy of the treatment they received at the end of each treatment phase. Overall, significantly more patients rated sumatriptan (100 mg) than placebo as 'good' or 'excellent' (64% *vs.* 21%, $p<0.0001$). At the end of the study, patients stated the treatment they preferred. Sixty-four per cent of patients preferred sumatriptan, 15% preferred placebo and 21% expressed no preference. Of those who expressed a preference, 81% preferred sumatriptan.

Table 3 Efficacy of sumatriptan (100 mg) and placebo in treating migraine attacks occurring inside and outside the menstrual window: proportion of patients reporting headache relief, complete headache relief, headache improvement and complete headache improvement. Patients who treated their first attack in the two phases of the study with sumatriptan and placebo

Endpoint	Percentage of patients					
	Inside menstrual window			Outside menstrual window		
	Sumatriptan 100 mg	Placebo	*p*-value	Sumatriptan 100 mg	Placebo	*p*-value
Headache relief (Grade 3/2 to Grade 1/0)	67 (*n*=39)	33 (*n*=39)	0.0072	79 (*n*=41)	31 (*n*=41)	<0.0001
Complete headache relief (Grade 3/2 to Grade 0)	49 (*n*=39)	10 (*n*=39)	0.0001	60 (*n*=41)	9 (*n*=41)	<0.0001
Headache improvement (≥1 grade)	71 (*n*=48)	33 (*n*=48)	0.0003	77 (*n*=48)	33 (*n*=48)	0.0001
Complete headache improvement (Grade 1/2/3 to Grade 0)	54 (*n*=48)	15 (*n*=48)	<0.0001	60 (*n*=48)	21 (*n*=48)	0.0009

Safety

Eighty-three patients (72%) reported 368 adverse events during the study. More patients reported adverse events when they were receiving sumatriptan (100 mg) (64%) than when they were receiving placebo (44%). The most common types of adverse event were associated with the nervous and digestive systems. However, only 8 patients (7%) withdrew due to adverse events.

Discussion

This study provides evidence for two issues that are clinically relevant for the management of migraine in the clinic. Firstly, pure menstrual migraine, and menstrually related migraine were found to occur in fewer patients than originally thought. Secondly, oral sumatriptan (100 mg) is an effective and well tolerated acute treatment for the spectrum of menstrual migraines and menstrually associated migraines experienced by patients.

In the present study, patients were recruited who had a self-reported history of menstrually related migraine, with a definition of ≥80% of their attacks occurring during their menstrual periods for the previous 6 months. The average migraine history was 15 years, with the vast majority of attacks lasting for 1 day or more. Although most patients were using acute medications, the majority did not find them effective. During the study, patients reported frequent migraine attacks (average 2.5 per month).

During the prospective reporting of migraine attacks during the study, only 11% of patients reported a pattern of menstrually related migraine as defined in the study protocol. Three groups of patients could be identified from the diary cards: a small group (11%) who had menstrually related migraine; a larger group (41%) who showed a consistent pattern of clustering of migraine attacks within the menstrual window but who had many attacks at other times in the menstrual cycle; and the largest group (48%) who had the majority of their attacks outside the menstrual period. It is clear that there is a considerable and variable group of women in whom there is a clinically relevant association between menstruation and migraine attacks. The clinical profile of these patients may be complex, with multiple triggers acting in combination.

The over-reporting by patients of a link between menstruation and migraine has been noted previously. Definitions for pure and menstrually-related migraine were proposed of 100% and ≥80% of attacks, respectively, both during the period from −2 to +3 days from the onset of menstruation [6, 25]. Prospectively collected data from the present study indicate that a self-reported association of migraine attacks with menstruation covers a spectrum of illness, from patients with attacks solely associated with the menstrual period (pure menstrual migraine), to menstrually related migraine, to those with attacks that occur primarily outside, but with a few attacks occurring within the menstrual period. Support for this comes from two separate sources. Firstly, several studies have indicated that menstruating women experience migraine attacks both inside and outside the menstrual period [10, 11, 14]. Secondly, recent studies have demonstrated that severely affected migraine sufferers have multiple clinical presentations of their migraine attacks, from true migraine, through migrainous headache to tension-type headache.

However, this entire spectrum of headache may be a manifestation of the migraine process [26].

Data from the present study showed that oral sumatriptan (100 mg) was an effective and well tolerated acute treatment for patients with migraine attacks occurring inside and outside the menstrual period. The proportions of patients reporting headache relief, complete headache relief, headache improvement and complete headache improvement were slightly less for attacks occurring inside the menstrual period than for those occurring outside the period. However, in all cases, sumatriptan (100 mg) was significantly more effective than placebo and the response rates were similar to those described previously for this regimen of the drug [27]. The 4-hour endpoint was used because the 2-hour time period had not been established as optimal to record efficacy in migraine studies at the time of the study. Sumatriptan (100 mg) was generally well tolerated. The incidence of reported adverse events was relatively high for both sumatriptan and placebo, and may indicate a generally poor level of health and quality of life in these patients due to pre-menstrual symptoms and frequent migraine attacks. Most previous studies of triptans in menstrual migraine have evaluated their efficacy in treating attacks occurring only inside the menstrual period [16–21]. The present study demonstrated the efficacy of oral sumatriptan (100 mg) for the spectrum of migraine attacks in a population of patients self-reporting with menstrually related migraine. To support this, recent studies have shown that oral sumatriptan (50 mg) is an effective treatment for the spectrum of headaches reported by the general population of migraine sufferers [26].

This study does have several limitations. The definition of menstrually related migraine (self-report of >80% of menstrual attacks falling within the menstrual window in the previous 6 months) is questionable and, perhaps not surprisingly, only a few women (11%) fulfilled this criterion in the prospective study. The latest criterion published by the IHS for menstrually related migraine without aura is: "attacks occur on day 1±2 of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle" [28]. MacGregor's criterion is similar, from –2 to +3 days with respect to the first day of bleeding [6, 25]. From this, the most used criterion to define menstrually related migraine may be the constant or almost constant occurrence of menstrual attacks, regardless of the number of non-menstrual attacks. The menstrual window used in this study (8 days) may be large enough to include attacks pathophysiologically and perhaps clinically different from true menstrual attacks. Despite these caveats, the study demonstrated a disparity between what the patients subjectively reported and the data that were collected prospectively.

In this study, a high percentage of women (49%) suffered from migraine with and without aura. Classically, menstrually related migraine is without aura, as defined by the IHS [28]. The high prevalence of women suffering from migraine with aura in this study may have affected the results. Finally, the primary study time point for assessment (4 hours) is not currently used in migraine studies, 2 hours being regarded as the optimal time point [29].

Clinical implications

Further studies are necessary to explore the treatment of migraine headaches occurring inside and outside the menstrual period. However, some general principles can be proposed. Migraine is a disabling condition, irrespective of its time of onset [30]. Where patients have migraine attacks that occur both inside and outside the menstrual period, they can probably be managed using standard acute therapies (e.g., triptans and analgesic plus anti-emetic combinations). Both oral and subcutaneous sumatriptan formulations provide effective treatment, although the maximal oral dose of sumatriptan was used in the present study. The efficacy of lower oral doses of sumatriptan (50 mg and 25 mg) is not known, but may be less than that reported here for the 100 mg dose in this group of patients [31]. Oestrogen supplements may be best reserved for patients with migraine attacks that occur during menstruation only (pure menstrual migraine).

In conclusion, most women who self-report menstrually related migraine do not have the condition, but experience a spectrum of migraine attacks both inside and outside their menstrual periods. Oral sumatriptan (100 mg) is an effective and well tolerated acute treatment for all the migraine attacks experienced by these patients.

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