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Treatment with sumatriptan 50 mg in the mild phase of migraine attacks in patients with infrequent attacks: a randomised, double-blind, placebo-controlled study

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Abstract Most migraine patients with infrequent attacks are currently not treated with migraine-specific medication such as triptans. The response of these patients to triptans is unknown. The objective of this study was to investigate the efficacy and tolerability of sumatriptan 50 mg *vs.* placebo in migraine patents with infrequent migraine attacks when medication is taken during the mild phase of an attack. The study design was double-blind, placebo-controlled, parallel-group and randomised. Migraine patients were recruited by general practitioners and referred to one of 4 study centres. Additional patients were recruited by advertising. The patients were eligible for the study if they had between 6 and 12 migraine attacks with or without aura per year. The patients were instructed to take the medication during the mild phase of a single attack. The primary efficacy measure was the percentage of patients pain-free after 2 h. Forty-six percent of treated attacks were moderate or severe. In the intention-to-treat analysis, sumatriptan was superior (20/51 patients were pain-free) to placebo (8/47 patients pain-free) (p=0.03). Adverse events (AEs) occurred more frequently after sumatriptan (40%) than after placebo (13%) (p=0.003) and most AEs were mild or moderate. In this migraine population with infrequent attacks, sumatriptan was superior to placebo and was generally well tolerated.

Keywords Migraine • Sumatriptan • Mild phase • Controlled clinical trial

Introduction

Sumatriptan and other triptans have proved useful in the treatment of migraine attacks, both with respect to efficacy and tolerability [1–5]. In the majority of randomised controlled trials on triptans, migraine patients with a high frequency of attacks, typically more than one per month, were included, and treatment was initiated when headache was moderate or severe. This group of patients, rather experienced with migraine, was targeted, because a reasonably brief time between screening and intake of study

drug, as well as a high degree of certainty that genuine migraine attacks and not other types of headache was treated, have been priorities. This strategy leaves a group of patients having less frequent attacks with less substantial documentation of efficacy and tolerability of triptans. The same patient group is likely to be a major fraction of the large part of migraine patients that do not treat attacks with triptans [6], and the poor evidence of benefit from triptans in these patients may be one of several motives for doctors recommending alternative drugs such as over-the-counter drugs for their migraine. In addition, these patients often do not consult for migraine.

As frequently pointed out in the recent literature, there may be good arguments for treating migraine attacks while the headache intensity is still mild [7, 8], although this has been challenged [9]. Retrospective analyses of sumatriptan data have suggested that treatment in the mild headache phase is associated with higher pain-free rates than when treatment is initiated at higher headache intensity [10] and a prospective study showed that sumatriptan was effective when given at the first sign of pain [11]. Finally, it has been suggested that central sensitisation may occur quickly during migraine attacks, being detectable as allodynia on the skin of the head [12], and that such sensitisation diminishes the triptan effect [8]. Finally, using an analogy to episodic and chronic tension-type headache where clearly more signs of central sensitisation are found in the chronic than in the episodic form [13], it may be speculated that migraine patients with rare attacks would experience excellent effect from triptans.

We therefore conducted a prospective randomised placebo-controlled study on the efficacy and tolerability of sumatriptan in the mild phase of migraine in patients with not more than 6–12 attacks per year.

Patients and methods

Inclusion and exclusion criteria

Patients were eligible for the study if they were between 18 and 65 years of age, suffered from migraine with or without aura as defined by the 1988 International Headache Society criteria (IHS) [14] for at least a year, had a history of 6–12 migraine attacks per year, had the experience that the headache became moderate or severe following a mild phase, were able to differentiate migraine from other headaches and had not treated a migraine with a triptan within the last 6 months.

Patients were excluded if they had uncontrolled hypertension (diastolic blood pressure >95 mmHg or systolic blood pressure >160 mmHg); had cardiovascular disease; suffered from chronic tension-type headache [14]; had ophthalmoplegic, basilar and hemiplegic migraine; or had suspected or confirmed cerebrovascular or cardiovascular disease.

Study procedures

Patients were recruited by general practitioners (GPs) while seeking assistance for headaches or other problem. The patients were screened using a questionnaire based on the IHS criteria, based on which the patients were screened. The GPs were instructed to check the inclusion and exclusion criteria to make sure the patients were eligible to enter the study. The GPs then faxed names and addresses to the headache centre. All the patients were hereafter contacted by phone and re-screened. Due to a slow inclusion rate, advertising in local newspapers was initiated to provide a sufficient number of patients.

Patients who fulfilled the inclusion and exclusion criteria at the screening visit were randomised to receive either sumatriptan 50 mg or placebo in the ratio 1:1. They were randomised in blocks of 6. After randomisation the patients had 5 months to treat a migraine attack. They were instructed to treat the attack within one hour after the attack started, but only if the attack was still in the mild headache phase. Patients who experienced complete pain relief two hours after intake of study medication could take a second dose if they experienced a recurrent headache that was moderate to severe 2–24 h after intake of the first dose. Alternatively, they could use their usual medication.

Patients who did not experience complete pain relief after 2 h could take rescue medication. Triptans or ergotamine were not allowed within 24 h after test medication.

Efficacy and tolerability measures

The primary efficacy measure was the percentage of patients pain-free two hours after intake of study medication.

The secondary efficacy measures were:

- The percentage of patients who were pain-free 30 min and 1 h after intake of study medication.
- The percentage of patients who were pain-free 2–24 h after intake of study medication.
- The percentage of patients without accompanying symptoms (nausea, vomiting, phonophobia and photophobia) 30 min, 1 and 2 h after intake of study medication.
- The percentage of patients using rescue medication from 2 to 24 h.
- The percentage of patients who used a second dose of study medication or other anti-migraine drug within 24 h of the first dose of study medication.
- The percentage of patients satisfied with study medication.
- Number of hours away from work/education or social activities.
- The occurrence and severity (mild, moderate or severe) of adverse events (AEs).

Statistical methods

A sample size of 58 subjects in each treatment group was supposed to give at least 80% power (β) under the assumption that 25% of patients given placebo would be pain-free at 2 h *vs*. 50%

given sumatriptan. A two-sided test and a significance level (α) at 5% were assumed. Furthermore, it was assumed that approximately 20% of the subjects would not be able to treat a migraine attack during the study period. Hence it would be necessary to randomise a total of 146 subjects.

Statistical analyses of the proportion of patients pain-free and other efficacy measures were done with Fisher's exact test. $p<0.05$ was chosen as the significance level.

The safety population included all subjects who took study medication. The intention-to-treat (ITT) population included subjects from the safety population who provided at least one post-dose efficacy assessment. Missing data from the 30-min, 1- and 2-h time points were not imputed. The ITT population consisted of patients treated with investigational product and who had efficacy data.

Ethical approval

The study protocol was approved by the local ethics committees. Written, informed consent was obtained prior to inclusion.

Results

Patients' characteristics and recruitment

Disposition of study subjects is shown in Figure 1. One hundred and fifty-eight patients were screened and 150 patients were randomised. Of these, 49 (33%) patients did not receive study medication [17 lost to follow-up, and 32 had no opportunity to treat in the 5 months study period (Fig. 1)].

The demographic and baseline characteristics in the ITT population are shown in Table 1.

Treated attacks

In the placebo group there were 11 attacks of migraine with aura and 33 attacks of migraine without aura (2 attacks had missing aura information) whereas in the sumatriptan group there were 12 attacks of migraine with aura and 40 attacks of migraine without aura.

A summary of headache pain scores (no pain, mild, moderate and severe) at the start of the headache and before the first dose for treated attacks is shown in Table 2. Before the first dose, 46% of subjects (45 of 98) had moderate or severe pain across both treatment groups.

In the placebo group 6 patients (13%) were severely impaired (2/5) or required bed rest (4/1)) whereas this was the case for 6 patients (12%) in the sumatriptan group. The scale was a 5-point scale: not at all, mild, moderate, severe, bed rest required.

Before intake of study medication 69% in the placebo group and 57% in the sumatriptan group were suffering

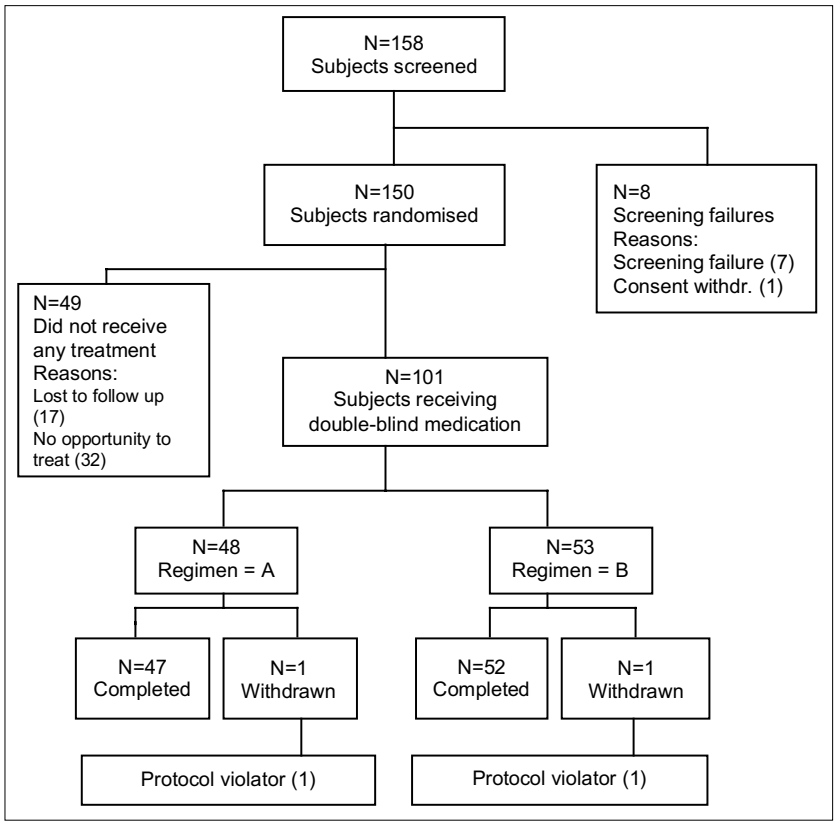

Fig. 1 Disposition of study subjects

Table 1 Demographics and baseline characteristics (ITT population)

		Placebo (n=48)	Sumatriptan 50 mg (n=52)
Number of subjects	Total	48	53
Males	Number (%)	8 (17%)	14 (26%)
Females	Number (%)	40 (83%)	39 (74%)
Age			
Males [years]	Mean (SD)	48 (10)	40 (12)
Females [years]	Mean (SD)	36 (11)	36 (9)
Migraine with aura	Number (%)	4 (8%)	7 (13%)
Migraine without aura	Number (%)	40 (83%)	41 (77%)
Migraine with and without aura	Number (%)	4 (8%)	5 (9%)
Previous triptans	Number (%)	5 (10%)	7 (13%)
Concurrent medications	Number (%)	36 (75%)	31 (59%)

Table 2 Summary of the level of pain (ITT population)

Time	Placebo (n=48)				Sumatriptan 50 mg (n=53)			
	No pain	Mild	Moderate	Severe	No pain	Mild	Moderate	Severe
At migraine start	3	36	6	1		45	7	
Missing values	2				1			
Before first dose		22	22	2		31	21	
Missing values	2				1			
30 minutes after	1	15	26	3	3	21	26	2
Missing values	3				1			
1 hour after	3	19	17	6	7	18	21	4
Missing values	3				3			
2 hours after	8	9	18	10	20	14	12	5
Missing values	3				2			

Missing values (MV) not imputed in table

from nausea. For photophobia the percentages were 80% and 61%, and for phonophobia the percentages were 49% and 35%, respectively.

Efficacy

In the ITT population 20 of 51 (39%) patients treated with sumatriptan were pain-free after 2 h whereas this was the case in 8 of 45 (18%) patients treated with placebo [difference 21%; 95% confidence interval (CI): +4%–+39%; p=0.03, Fisher's exact test, see Table 2]. In the per protocol (PP) population (the patients with mild headache) 14 of 30 (47%) patients treated with sumatriptan were pain-free after 2 h whereas this was the case in 6 of 22 (27%) patients treated with placebo (difference 20%; 95% CI: –6%–+45%; p=0.3, Fisher's exact test). In the ITT and PP population there was no difference between treatment groups for pain-free after 30 min and 1 h, and no difference concerning photo- and phonophobia, and nausea.

In the ITT population more patients had a sustained pain-free response after sumatriptan (15/46) (33%) than after placebo (5/39) (13%) (difference 20%, 95% CI +3%–+37%; p=0.06, Fisher's exact test); in the PP population the difference was 23% (sumatriptan (11/28) (39%) and placebo (3/19) (16%) (95%CI: –1%–+48%; p=0.16, Fisher's exact test).

Study medication satisfaction

In the ITT population 22/53 patients (42%) treated with sumatriptan were satisfied or very satisfied with the study medication in general whereas this was only the case in

Table 3 Patients with AEs in the ITT population

Treatment		Severity		
		Mild	Moderate	Severe
Sumatriptan 50 mg	Patients with AEs (n=27)	13	10	4
	Number of AEs 44	19	19	6
Placebo	Patients with AEs (n=7)	1	5	1
	Number of AEs 10	1	8	1

7/48 (15%) of patients treated with placebo. In the PP population 16/31 patients (52%) treated with sumatriptan were satisfied or very satisfied with the study medication in general whereas this was only the case in 5/22 (23%) of patients treated with placebo.

In the ITT population the median number of hours away from work/education was 4.8 h (min-max: 0.5–12.0 h) in the placebo group and 5.3 h (min-max: 1.0–16.0 h) in the sumatriptan group. Median hours away from social activity was 6.5 h (min-max: 1.5–40.0 h) in the placebo group and 3.0 h (min-max: 1.0–48.0 h) in the sumatriptan group.

Tolerability

In total there were 54 AEs reported, 10 after placebo and 44 after sumatriptan (see Table 3). The number of patients with any AE was higher after sumatriptan (27/53, 51%) than after placebo (7/48, 15%) (difference 36%; 95%CI: +20%–+53%; p=0.003; Fisher's exact test). The most common AEs were nausea (n=5), paraesthesia (n=4), fatigue (n=3) and chest pressure sensation (n=2). Most AEs were mild to moderate and of short duration.

Discussion

Methodological considerations

The aim of this study was to evaluate the efficacy and tolerability of sumatriptan 50 mg in a migraine population normally not being treated with a triptan. Only 10%–13% in the study population had previously used a triptan. The inclusion criterion was infrequent migraine of 6–12 attacks per year. The study population was therefore recruited by GPs and by advertisement. As shown by the time absent from work (median 5 h with maximum up to 16 h) and hours away from social activity (median 6 and 3 h in the placebo and sumatriptan groups, respectively, with maximum of 40–48 h), the societal impact of migraine is considerable in this selected patient population, even when they could use rescue medication after 2 h.

In addition, based on recent experience [7, 10, 11, 17, 18] demonstrating a higher treatment response (43% with 2.5 mg zolmitripan [7], from 51% to 66% with 50–100 mg sumatriptan [11, 17, 19] and 70% with 10 mg rizatriptan [18]) when treating with a triptan in the mild phase of a migraine attack, we instructed the patients to treat in the mild phase of their attacks. In contrast, previous trials [1–5] instructed the patients to wait until the pain was moderate or severe and subsequently low response rates for pain-free after 2 h, i.e., 28% [1] were found. In real life patients are also more likely to start treatment at the beginning of a migraine attack.

The patients were instructed to treat the migraine attack within one hour of its start, but only if the attack was still in the mild headache phase. Despite this, almost half the patients treated an attack when the headache was moderate or severe (Table 2). The most likely explanation is that this was not the kind of patient normally participating in randomised controlled trials. They were not accustomed to filling out headache diaries and being treated as instructed in a clinical trial.

Results of this study

In this study 38% (95CI: 25%–53%) of patients in the ITT population were pain-free after 2 h. In studies with sumatriptan 50 mg with similar designs 51% [17], 50% [11] and 51% [19] of patients were pain-free after 2 h, but in these studies all patients were treated in the mild phase of headache. In patients treating moderate/severe attack the pain-free rate was 28% with sumatriptan 50 mg [1]. In our study half the patients treated moderate/severe attacks and the results for pain-free are in between the results from these studies [1, 11, 17, 19].

Our hypothesis that these patients with relatively infrequent migraine attacks would be easier to treat could thus not be proved. Furthermore it was surprising that 49 patients (almost 33%) did not treat an attack within the

timelines, revealing that this patient group is reluctant to treat their migraines with migraine-specific drugs before they are sure that it is a real migraine attack.

In terms of tolerability, sumatriptan resulted in more AEs than placebo. Most AEs were, however, mild and moderate.

In conclusion, sumatriptan 50 mg is effective in treating migraine patients with a frequency of less than 1 attack per month, and sumatriptan is well tolerated. The efficacy of sumatriptan, the profile of AEs and social impact in this study are similar to other studies with more severely afflicted patients.

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