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Sumatriptan (50 and 100 mg) in repeated migraine attacks: a patient preference study

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Abtract Oral sumatriptan in 100-mg tablets is an effective and well tolerated treatment for the acute migraine attack. Since the launch of that dose, further studies have suggested good efficacy also for lower doses. This Italian multicentre study aimed at evaluating patient preference between the 50- and 100-mg does for acute treatment of migraine. Data on efficacy and safety are provided as secondary end points of this trial. The study design is on open basis: the patients treated their first 3 migraine attacks with 50 mg sumatriptan and then were able to choose whether to increase the dose to 100 mg or to continue with the initial treatment for the next 3 attacks. Two hundred one patients treated at least 3 attacks and 182 treated 6 attacks: 68% of the patients, after the third attack, preferred to continue with 50-mg sumatriptan tablets, while 32% preferred to switch to the 100-mg dose. In the first 3 attacks treated with 50 mg, 60% of patients improved at 2 hours and 72% at 4 hours after the first dose. In the set of patients that preferred to use 100 mg for the second block of 3 attacks (32%), the improvement at 2 and 4 hours after the dose was respectively 34% and 48%. Minor adverse events were reported by 15% of the patients. We conclude that less than one-third of patients treated with sumatriptan needs the 100-mg dose.

Key words Oral sumatriptan • Patient preference study

Introduction

Sumatriptan is a 5-$HT_{1b/d}$ receptor agonist [1] that mediates selective vasoconstriction of cranial blood vessels and also has inhibitory effects on trigeminal neurons, blocking plasma extravasation from blood vessels in dura mater [2]. Cranial blood vessel dilatation and plasma extravasation are believed to be involved in the pathophysiology of migraine attacks. Clinical studies have demonstrated that a 100-mg oral dose of sumatriptan is highly effective and well tolerated in the acute treatment of migraine with 67%–75% of patients having headache relief at 4 h [3, 4]. Sumatriptan in 100-mg tablets was marketed early in 1991; later experience suggested good efficacy of a low oral dose (50 mg). This evidence has been confirmed in a recent clinical trial, in which the 50-mg oral dose relieved headache within 2 h in 70% of patients affected by migraine without aura; 66% of the patients were free from headache [5].

This study aimed at evaluating patient preference in a situation that mimics, as closely as possible, normal clinical decision making. Efficacy and safety data are also provided for each dose.

Patients and methods

Patients

Appropriate ethics and regulatory approvals were obtained at each centre. Patients gave written informed consent prior to entering the

study. The study met Good Clinical Practice criteria. Patients, aged 18–65 years, were eligible for the study if they met International Headache Society (IHS) criteria for migraine with or without aura [6] and if they had experienced migraine attacks of severe to moderate intensity for at least one year. Ergotamine migraine prophylaxis, drug abuse, cardiovascular disorders, severe diseases, pregnancy and lactation were exclusion criteria. Patient preference was assessed using a 5-point scale (1, ineffective; 2, poor; 3, sufficient; 4, good; 5, excellent). Headache was assessed by patients using a 4-point pain scale (0, none; 1, mild; 2, moderate; 3, severe).

Methods

This was a multicentre, open design, dose-titration study to evaluate dosing of sumatriptan (50 mg and 100 mg) in the acute treatment of migraine. Patients attended the clinic for a pre-treatment evaluation, where demographic data, medical and migraine history, blood pressure and heart rate were recorded. Patients were given diary cards to register the course of attacks, the severity of pain, the associated symptoms, and the clinical disability at 2 and 4 h. The patient was also asked to register when rescue medication was used and when the headache recurred. Patients were instructed to take the study medication (50 mg sumatriptan) for the first three attacks (phase 1). If no relief was achieved at 4 h, patients were allowed to take a rescue medication. If relief was achieved at 4 h, but a new attack arose within 24 h, the patients were instructed to treat the recurrence with the same dose of study medication. After the third attack, the patients returned to the centre where they were counselled before deciding whether to take the same dose for the next 3 attacks (phase 2), or to increase the dose to 100 mg.

Statistical analysis

Patient preference is reported as the number and percentage of patients who preferred the dose of 50 mg or 100 mg after the third attack. The efficacy analysis reports the number of attacks in which headache relief has been obtained at 2 and 4 h after the drug administration. Headache relief was defined as a reduction in severity from grade 3 (severe) or 2 (moderate) to grade 1 (mild) or 0 (none). Patients who took rescue medication with the 4-hour post-dose period were counted as treatment failure. The number of patients reporting nausea, vomiting and photo/phonophobia was assessed at 4 hours after the dose. The safety population included all patients who treated at least 1 attack with the study medication. Adverse events have been tabulated by body system and symptoms for the two different treatment groups.

Results

Two hundred twenty-five (225) patients entered the study (Table 1) and treated at least one attack with the study medication. One patient did not complete the diary card for the first attack, so the efficacy population for attack one is 224. Between attack one and the second phase of the study (attack 4), 35 patients withdrew from the study. The reasons for withdrawal are: adverse events (n = 11); lack of efficacy (n = 6); failed to return to the visit (n = 14); and other reasons (n = 4). During phase 1 (attacks 1–3), 201 patients treated all three attacks, and 182 completed the study with the treatment of all 6 attacks (Table 2).

Of the 201 patients that treated all three attacks, 11 withdrew from the study: one for lack of efficacy, and 10 failed to return to the study centre. Of the remaining patients, 130 (68%) decided to continue with the same dose

Table 1 Demographic and clinical characteristics of the 225 patients who entered the study (safety population)

Age, years	38.0	(10.6, 17–68)[a]
Weight, kg	64.0	(11.6, 44–100)[a]
Height, cm	165.0	(8.0, 148–195)[a]
Males, n (%)	56	(25)
Migraine history, months	120[b]	
Attack frequency, number of patients (%)		
1 per month	14	(6.2)
2 per month	43	(19.1)
3 per month	46	(20.5)
≥ 4 per month	122	(54.2)
Pain intensity, number of patients (%)		
Mild	0	
Moderate	64	(28)
Severe	161	(72)

[a] Mean (SD, range)
[b] Median

Table 2 Patients' participation in the two study phases, and preferences for the 50-mg or 100-mg dose of sumatriptan

	Patients, n		
Study phase	Sumatriptan 50 mg	Sumatriptan 100 mg	Total
Phase 1			
Attack 1	224[a]	–	224
Attack 2	212	–	212
Attack 3	201	–	201
Phase 2			
Attack 4	130 (68)[b]	60 (32)	190
Attack 5	130 (69)	58 (31)	188
Attack 6	125 (69)	57 (31)	182

[a] One additional patient treated 3 attacks but did not maintain a diary; [b] Values in parentheses are percentages

(50 mg) and 60 (32%) decided to switch to 100 mg. The main reasons for switching to the high dose were: lack of efficacy (90%); recurrence (3%) and slow onset of efficacy (7%). After the treatment of the third attack, the patients' opinions about the 50-mg tablet treatment were: ineffective, 3%; poor, 19%; sufficient, 35%; good, 28% and excellent, 15% (Fig. 1).

In study phase 1, the patients treated a total of 569 attacks with initial severity of grade 3 or 2; 60% of the attacks improved at 2 h and 72% at 4 h (Fig. 2). Among the patients continuing study phase 2 with the 50-mg dose, 73% of attacks improved at 2 hours and 83% at 4 hours. In the group who treated the 3 phase-2 attacks with 100-mg tablets, 34% of attacks improved at 2 hours and 48% at 4 hours (Fig. 3).

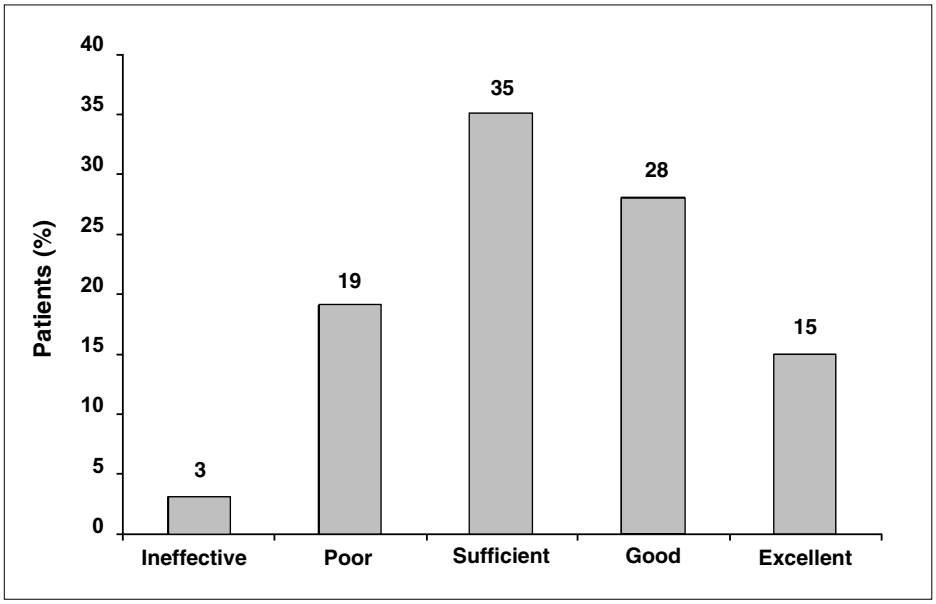


Fig. 1 Patients' opinions of the 50-mg dose after phase 1 of the study

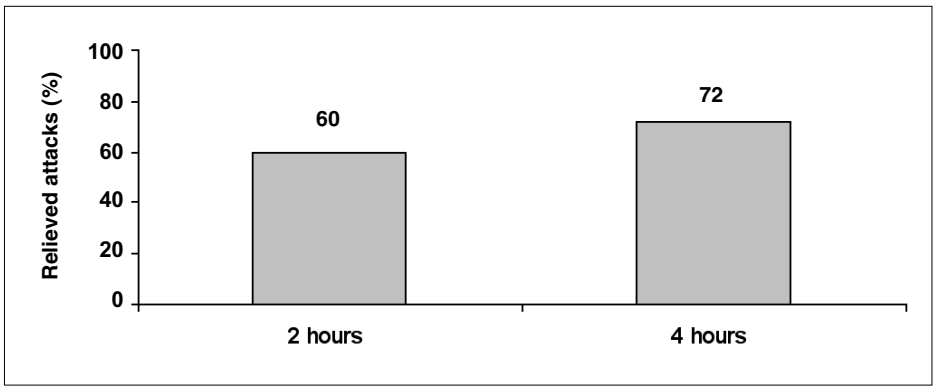
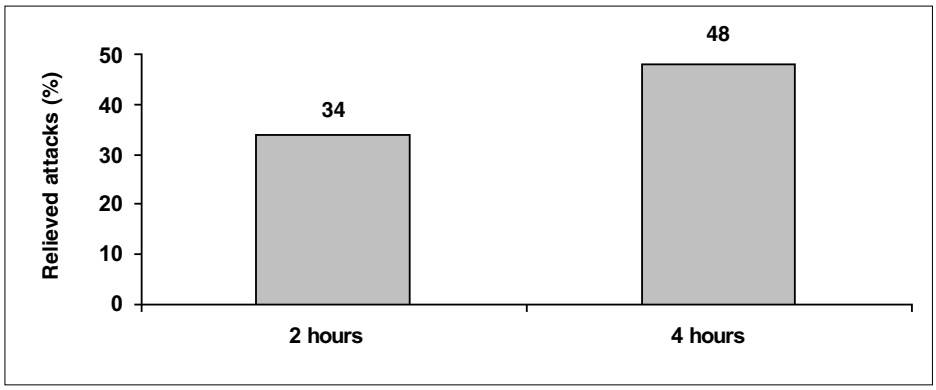


Fig. 2 Headache relief at 2 and 4 hours after treatment with 50 mg sumatriptan in phase 1 (n = 569)

Fig. 3 Headache relief at 2 and 4 hours after treatment with 100 mg sumatriptan in phase 2 (n = 175)



Pretreatment nausea or vomiting was reported in 58% and photo- or phonophobia in 68% of patients during the attacks in phase 1 (Fig. 4). At 2 and 4 hours post-dose, the attacks with nausea or vomiting were 22% and 17%, respectively. At these time points, the attacks associated with photo- or phonophobia were 32% and 28%, respectively. Similar results were found in study phase 2 among those patients who chose the 100-mg dose (Fig. 5).

Rescue medicine was seldom necessary during the study. Of all the headache attacks treated with the 50-mg dose, rescue medication was resorted to in only 5% of cases. For patients choosing the 100-mg dose, rescue medicine was used in 6% of cases.

The rate of headache recurrence – defined as a new attack starting 4–24 h after sumatriptan treatment – was 36% in the group of patients taking 100 mg (phase 2, n = 70) and 27% in all the attacks treated with 50 mg.

No serious adverse events were recorded during the study. Minor adverse events were recorded by 15% of patients, irrespective of sumatriptan dose (Table 3). The majority of these adverse events was mild to moderate and short-lasting, and resolved spontaneously. The events more frequently reported were similar to those described in the previous studies, such as heaviness, nausea, vomiting, tightness, vertigo and asthenia. No significant changes in blood pressure or heart rate were found.

Discussion

This open study aimed to evaluate patients' preferences for 2 different doses of sumatriptan (50 mg and 100 mg). It is well known that patients have attempted to break the 100-mg tablets in order to assume a half dose. In Italy, the 50-mg dose has been introduced recently so that there is little clinical experience with this dose. The present study has been designed to mimic actual patients' behaviour when they are allowed to choose between two different doses of the same drug. The patient preference evaluation is not a common parameter in clinical trials, but it is frequently used in migraine studies. Patient behaviour is important for drug compliance: sometimes a low response rate to migraine treatments is mainly due to lack of compliance rather than to poor drug effectiveness. The patient preference evaluation has been used in the past to evaluate prophylaxis treatments [7], but now is also widely used for acute attacks [8, 9]. This end-point has also been applied in a trial aimed to compare patients' preferences between oral and subcutaneous sumatriptan in migraine [10]. In the evaluation of the results, we must consider that the study design could lead to a spontaneous selection of patients entering phase 2. In the group of patients that preferred to continue with 50 mg, the headache relief rate might be higher than expected because of a predominance of satisfied patients; the opposite may be true for

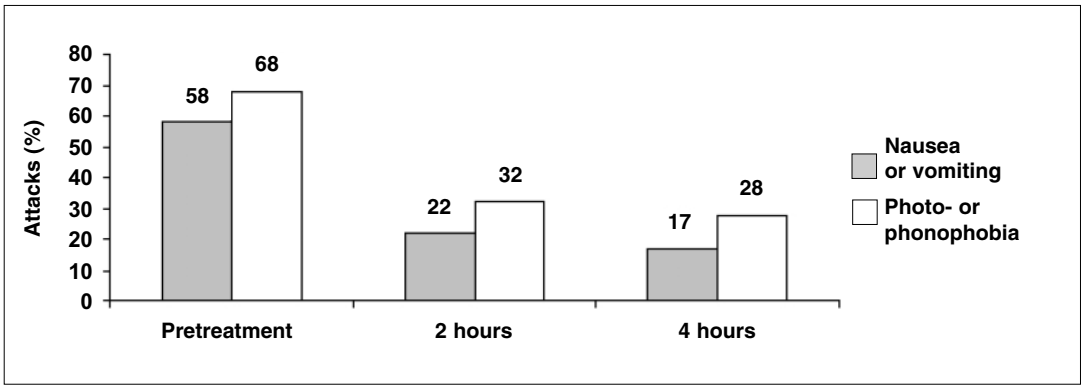


Fig. 4 Occurrence of headache-related symptoms before and after treatment with 50 mg sumatriptan during the 3 attacks of phase 1

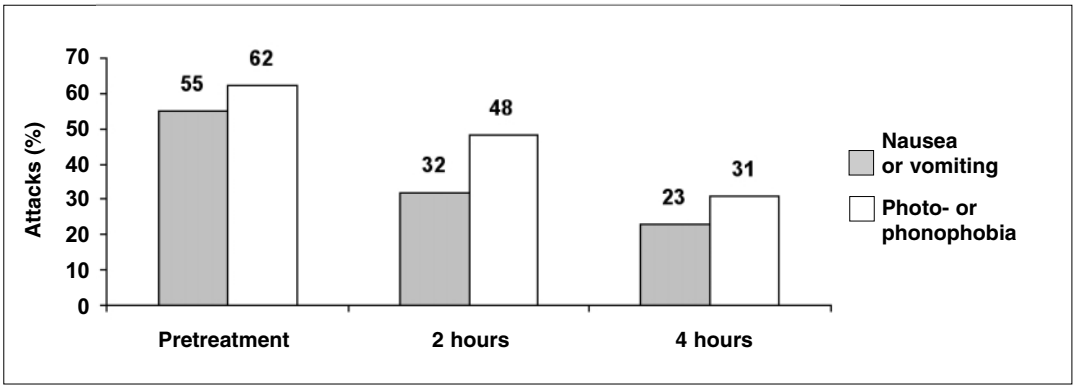


Fig. 5 Occurrence of headache-related symptoms before and after treatment with 100 mg sumatriptan during the 3 attacks of phase 2. A total of 175 headache attacks were thus treated

Table 3 Occurrence, n (%), of adverse events during headache attacks, according to sumatriptan dose and organ system

Adverse event	Sumatriptan, 50 mg (1022 attacks)	Sumatriptan, 100 mg (175 attacks)
Cardiovascular (Chest tightness, hypertension, tachycardia)	4 (< 1)	2 (< 1)
Ear, nose and throat (Pharynx tightness, burning)	6 (< 1)	0 (0)
Gastrointestinal (Vomiting, epigastric colic, nausea, constipation)	7 (< 1)	4 (< 2)
Stomatological (Xerostomia)	1 (< 1)	0 (0)
Musculoskeletal (Neck stiffness, cervicalgia)	4 (< 1)	1 (< 1)
Neurological (Asthenia, insomnia, poor vision, numbness, headache, tiredness, vertigo, heaviness in head, anxiety, dizziness, paraesthesia)	27 (3)	3 (2)
Respiratory (Difficulty in breathing, dyspnoea)	2 (< 1)	0 (0)
Dermatological (Sweat)	1 (< 1)	0 (0)
Miscellaneous (Hot/cold sensation, allergy, facial pain, generalized pain, flu)	20 (2)	1 (< 1)

the group of patients who switched to 100 mg, who may have been prevalently non-responders to sumatriptan.

Our study, in terms of patient preference, demonstrates that the 50-mg dose was chosen by a great number of patients (68%). Moreover, in the group of patients who switched to 100 mg (32%), the treatment was effective in 48%. These data are supported also by the small number of attacks that required a rescue medication (5% with 50 mg and 6% with 100 mg). The headache recurrence was 27% and 36% for attacks treated with 50 mg and 100 mg, respectively; this finding confirms the data reported in the literature [11].

We found a very low percentage of patients requiring rescue medication, reflecting the accuracy of patient selection at the study centres.

The typical associated symptoms, such as nausea, vomiting, and photo- and phonophobia, were relieved by 50 mg and 100 mg sumatriptan. Only 15% of patients reported adverse events of mild to moderate severity, lasting a short time and spontaneously well controlled. No severe adverse events were recorded. The most common symptoms reported were similar to those described in the early sumatriptan studies and included heaviness, nausea, tightness, vertigo and asthenia. No changes in blood pressure and heart rate were detected. We conclude that the two marketed doses of sumatriptan, 50 mg and 100 mg, can achieve a clinical response in 80% of patients, taking into account the therapeutic gain obtained with the higher dose, sequentially administered to the 50-mg non-responders. This design has probably mimicked the actual migraineurs' practice and behaviour. The preferred dose is 50 mg, but the higher dose of 100 mg is useful for patients who fail to repsond to the lower dose. From our study we can conclude that more than two-thirds of patients treated with 50 mg oral sumatriptan achieve control of the attacks. The 100-mg dose may be useful in patients who do not respond to the lower dose.

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