An Open Study of Self-administration of Subcutaneous Sumatriptan to Treat Successive Attacks of Acute Migraine

THE PORTUGUESE SUMATRIPTAN AUTO-INJECTOR STUDY GROUP
(See appendix for list of investigators’ names and addresses)

The efficacy and safety of single doses of 6 mg sumatriptan, self-administered subcutaneously by patients using an auto-injector, for the acute treatment of up to three successive attacks of migraine was investigated in a multicentre, open, uncontrolled study in which 178 patients were enrolled. At attack 1, there was an improvement in headache (from severe or moderate to mild or no headache) in 74% of patients at 1 h, and in 82% at 2 h. The incidence of symptoms associated with migraine was decreased after sumatriptan injection. Nausea, vomiting and photo/phonophobia were reported by 72, 54, and 85% of patients, respectively, before the injection to treat attack 1, but by only 22, 12 and 27%, respectively, 2 h after the injection. Migraine recurred within 24 h in 27% of patients, but in 89% of patients was effectively treated with a further dose of 6 mg sumatriptan. Results for attacks 2 and 3 were similar. About 40% of patients experienced at least one adverse event; most of these were mild or moderate in intensity and were transient. It is concluded that 6 mg sumatriptan, self-administered using an auto-injector, is an effective and well tolerated treatment for migraine. Sumatriptan was as effective at attack 3 as at attack 1, and there was no evidence of a change in the incidence or the nature of adverse events with successive uses of the drug.
The Portuguese Sumatriptan Auto-injector Study Group
Self-administration of subcutaneous sumatriptan

KEY WORDS: SUMATRIPTAN; MIGRAINE; SUBCUTANEOUS INJECTION; AUTO-INJECTOR.

INTRODUCTION

Migraine is a common disorder, with an estimated prevalence of about 6% in men and 17% in women. Although some patients respond to prophylactic therapy, for example with beta-blockers, calcium channel blockers, pizotifen or methysergide, most rely on acute treatment of the attacks when they occur. Acute therapies have included analgesics, non-steroidal anti-inflammatory agents, and ergot derivatives. Such therapies are often of limited efficacy or may have unacceptable side-effects.

Sumatriptan is an agonist at the vascular 5-HT1 receptor and has been shown to be effective and well tolerated in the acute treatment of migraine when administered by the oral, intranasal, intravenous or subcutaneous routes.

During an acute migraine attack many patients suffer nausea, vomiting or diarrhoea, which may limit the effectiveness of oral therapies. Subcutaneous doses of 1–8 mg sumatriptan have been shown to be effective and well tolerated, with a clear dose-response trend. A 6-mg subcutaneous dose effectively relieved migraine in 72% of patients within 60 min and, because it offers the best balance between efficacy and tolerability, has been selected as the standard therapeutic dose.

It is not practical for patients routinely to attend a clinic during a migraine attack, and a method of self-administration using a prefilled auto-injector device has been developed. In a multinational study of 235 patients, 77% of patients who used the sumatriptan 6 mg auto-injector reported relief of headache 1 h after dosing in comparison with 26% of patients who took placebo. After 2 h the response rates had risen to 83% and 30% for sumatriptan and placebo, respectively. Sumatriptan was also more effective than placebo in relieving vomiting, nausea, photophobia and phonophobia, and enabled patients to return to work or resume normal activities earlier.

The multicentre, open study reported here was carried out to assess the safety and efficacy of self-administered subcutaneous doses of 6 mg sumatriptan used to treat up to three successive migraine attacks.

PATIENTS AND METHODS

PATIENTS

Male and female patients aged 18–65 years with a history of moderate or severe migraine with or without aura were eligible for inclusion in the study. These patients were attending out-patient clinics. Migraine was diagnosed according to the criteria of the International Headache Society. Patients were excluded from the study if they had a history, or evidence, of ischaemic heart disease, atherosclerotic disease, or any medical condition that might alter the metabolism, distribution and excretion of drugs (e.g. impaired hepatic function). Hypertensive patients with a supine diastolic blood pressure > 95 mm Hg were excluded, but those with mild to moderate hypertension were eligible for inclusion provided that blood pressure was well controlled (≤ 95 mm Hg). Calcium channel antagonists or beta-blockers were permitted for the control of hypertension. Patients were excluded if they had abused opiate analgesics, major tranquiliz-
ers, or ergotamines (≥ 10 mg/wk) within the previous year, or had a history of abuse of alcohol or other drugs. Pregnant or lactating women were excluded, and women of child-bearing age were included only if they were taking adequate contraceptive precautions.

The study conformed to Good Clinical Practice and to the Declaration of Helsinki (1964) as modified by the World Medical Assembly, Hong Kong (1989); before the study began, fully informed consent from all of the patients and ethics committee approval were obtained.

STUDY DESIGN
This open multicentre study was carried out in 29 hospitals in Portugal by neurologists and internal medicine investigating physicians. At the first pretreatment visit details of migraine history were recorded, and the patients were given a brief physical and neurological examination. A 12-lead ECG was recorded, along with blood pressure and heart rate. The investigator gave detailed instructions of how to complete the migraine diary cards. The details to be recorded on these cards included date and time of attack, time of dosing, severity of the headache, symptoms experienced, use of rescue medication, recurrence of the attack, and use of a second dose of sumatriptan.

At their second visit to the clinic the patients were issued with the diary cards and sufficient trial medication to treat up to three migraine attacks. Sumatriptan was to be the first treatment taken for a new attack and was administered by the patients using an auto-injector device which delivered the contents of a 0.5-ml syringe as a subcutaneous injection. The injection was self-administered into the thigh or upper arm. Each auto-injector was pre-filled with 0.5 ml of an isotonic solution containing 12 mg sumatriptan (as the succinate salt)/ml.

The patients were instructed to record details of the attacks on the diary cards. The severity of the headache was assessed using a four-point scale (0, none; 1, mild; 2, moderate; 3, severe) before and 1 and 2 h after dosing. Patients without a successful response (i.e. lowering of headache severity to grade 1 or 0) within 2 h of treatment were told to take rescue medication that did not contain ergotamine. (Patients were instructed not to take sumatriptan within 24 h of taking any medication containing ergotamine).

Patients who had a successful response (headache severity grade 0 or 1) within 2 h of treatment, but who then experienced a worsening or recurrence of headache (grade 2 or 3) between 2 and 24 h after the first injection, could take a second dose of sumatriptan, provided that there was a minimum of 2 h between doses. A maximum of two 6-mg injections was allowed in 24 h.

Patients returned to the clinic 5–7 weeks after the issue of medication. If three migraine attacks had been treated, the patients were considered to have completed the study. Patients who had not treated three attacks by this first follow-up visit returned after a further 5–7 weeks (end of study). All unused medication was collected from the patients at the final visit.

EVALUATION OF EFFICACY
The primary end-point of clinical efficacy was the number of patients with a change in headache severity from grade 3 or 2 to grade 1 or 0 within 2 h of treatment. Secondary end-points included the relief of nausea, vomiting, photophobia and phonophobia, the recurrence of the migraine attack within 24 h, the efficacy of the second dose of sumatriptan, the use of rescue medication, the number of days away from work due to the migraine attack, and the patient's overall opinion of treatment.
EVALUATION OF SAFETY
Safety and tolerability were assessed by measuring heart rate and blood pressure at the pretreatment and final follow-up visits. A 12-lead ECG was recorded for all patients at the pretreatment visit (unless one had been recorded in the preceding 3 months) and at the final follow-up visit for those patients who had reported an adverse event that involved chest symptoms. Adverse events were recorded at the follow-up visits. An adverse event was defined as any untoward clinical event that occurred during the trial, irrespective of its relationship to the study treatment. Investigators were asked to record their opinion about whether any event was unrelated or unlikely to be related to sumatriptan treatment, or was possibly, probably

TABLE 1
Demographic and clinical characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>178</td>
</tr>
<tr>
<td>Men</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Women</td>
<td>162 (91)</td>
</tr>
<tr>
<td>Mean age (years ± SD)</td>
<td>39 ± 8</td>
</tr>
<tr>
<td>Migraine history</td>
<td></td>
</tr>
<tr>
<td>Duration (years ± SD)</td>
<td>16 ± 9</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>&lt; 1 attack/month</td>
<td>7 (4)</td>
</tr>
<tr>
<td>1 – 3 attacks/month</td>
<td>124 (69)</td>
</tr>
<tr>
<td>Weekly</td>
<td>46 (26)</td>
</tr>
<tr>
<td>Daily</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Without aura</td>
<td>131 (73)</td>
</tr>
<tr>
<td>With aurab</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>32 (18)</td>
</tr>
<tr>
<td>Severe</td>
<td>145 (81)</td>
</tr>
<tr>
<td>Treatment in previous 6 monthsc</td>
<td></td>
</tr>
<tr>
<td>Ergotamines</td>
<td>54 (33)</td>
</tr>
<tr>
<td>Opiate analgesics</td>
<td>4 (2)</td>
</tr>
<tr>
<td>ASA, NSAID, NA</td>
<td>123 (71)</td>
</tr>
<tr>
<td>Other</td>
<td>60 (36)</td>
</tr>
</tbody>
</table>

aExcept where otherwise indicated.
bIncludes four patients with both types of migraine.
cASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drugs; NA, non-narcotic analgesics. Some of the patients had received more than one treatment.
or almost certainly drug-related. All events except those considered to be unrelated or unlikely to be related to sumatriptan were classed as drug-related.

**RESULTS**

**STUDY POPULATION**

The demographic and clinical characteristics of the study population are shown in Table 1. Of the 178 patients who entered the study, 28 did not treat an attack and four did not complete diary cards. Forty patients were withdrawn before the end of the study: 13 failed to return for follow-up, five withdrew because of lack of efficacy, 13 withdrew because of adverse events and nine gave other reasons. The maximum numbers of patients evaluable for the first, second and third attacks were 146, 123 and 89, respectively. At least 445 migraine attacks occurred among the total study population over the period of the trial, of which at least 377 (85%) were treated with sumatriptan.

**HEADACHE RELIEF**

Headache relief was defined as a reduction in severity from grade 3 or 2 to grade 1 or 0 (i.e. from severe or moderate headache to mild or no headache). At 1 h after taking sumatriptan during the first migraine attack, 74% of patients had experienced headache relief; at 2 h, 82% reported headache relief. The results for attacks 2 and 3 were very similar (Fig. 1).

**SYMPTOMS ASSOCIATED WITH MIGRAINE**

After the sumatriptan injection the incidences of nausea, vomiting and phonophobia were considerably decreased (Fig. 2). Reductions in all of these migraine-associated symptoms occurred within 1 h of treatment, and further decreases in incidence occurred 1–2 h after the sumatriptan injec-
Incidence of (a) nausea, (b) vomiting and (c) photo/phonophobia among patients before treatment and 1 and 2 h after self-administration, using an auto-injector device, of 6 mg sumatriptan subcutaneously.
Changes in symptoms were analysed using data on patients who had completed details both before treatment and at 2 h: for attack 1, of those patients who reported nausea, vomiting or photo/phonophobia before treatment, 74% (54/73), 70% (30/43) and 68% (60/88), respectively, recorded absence of the symptom at 2 h.

RECURRENT OF HEADACHE
The incidence of recurrence was defined as the number of patients who documented a recurrence of headache within 24 h, expressed as a percentage of the number of patients who reported an initial attack of grade 2 or 3 severity. No account was taken of whether the patient had used any rescue or non-study medication.

Migraine recurred in 27% (39/143) of patients at the first attack, in 23% (27/118) at the second attack and in 20% (17/87) at attack 3. The investigators questioned the patients about recurrence at the follow-up visits, and in more than 90% of cases the physician’s opinion about recurrence was in agreement with the results on the record card.

RELIEF OF RECURRENT HEADACHE WITH SUMATRIPTAN
For the first attack, 24 of the 39 patients (62%) who reported headache recurrence took a second dose of sumatriptan. Two hours after the second dose, 89% of the patients with severe or moderate headache (17/19) at the time of the second dose reported headache relief. Results were similar for the second and third attacks.

USE OF RESCUE MEDICATION
Rescue medication was used after 2 h by a minority of patients: 14% (21/146) for the first attack, 12% (15/123) for the second attack, and 9% (8/89) for the third attack. In approximately 50% of cases, patients took rescue medication following headache relief [i.e. when their headaches were mild or absent (grade 1 or 0)].

TIME UNABLE TO WORK
Nearly 70% (61/88) of patients reported that in the past they had been away from work for 1 day or more when they had a migraine attack. After treatment with sumatriptan this percentage was markedly decreased. Figure 3 shows the results for attack 1; results for the other two attacks were similar, with 73% (58/79), 75% (46/61) and 79% (38/48) of patients requiring no days away from work at attacks 1, 2 and 3, respectively.

PATIENTS’ OPINION OF TREATMENT
After each attack that had been treated with sumatriptan the patients were asked to record on the diary card their answer to the question “Would you continue to use the auto-injector?” More than 90% of patients responded positively (attack 1, 85/95 patients; attack 2, 66/70; attack 3, 52/55).

EVALUATION OF SAFETY
During the study, 44% of patients experienced one or more adverse event. All adverse events were resolved during the trial and the investigators classified none of them as serious. Overall, 13 of the patients who entered the study withdrew because of adverse events, which in all cases were assessed as being related to treatment with sumatriptan.

The percentages of patients having at least one adverse event during attacks 1, 2 and 3 were 42, 40 and 33% respectively, and over 90% of these adverse events were classified as drug-related by the investigators (Table 2). Most of the events were mild or moderate in intensity and transient. Adverse events were similar in nature and frequency to those reported in previous clinical trials with
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FIGURE 3

Days away from work due to a migraine attack. Patients were asked how many days they were unable to work in the past due to a migraine attack ('pretreatment', n = 88). During the trial the patients recorded time off work at each attack that was treated by self-administration, using an auto-injector device, of 6 mg sumatriptan subcutaneously. Data are shown only for attack 1 (n = 79).

TABLE 2

Incidence of adverse events reported during migraine attacks treated with sumatriptan

<table>
<thead>
<tr>
<th></th>
<th>Attack 1</th>
<th>Attack 2</th>
<th>Attack 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patientsa</td>
<td>146</td>
<td>123</td>
<td>89</td>
</tr>
<tr>
<td>Patients with one or more adverse events (%)</td>
<td>42</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Adverse events considered to be drug-related (%)</td>
<td>93</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Adverse events assessed as</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (%)</td>
<td>29</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>Moderate (%)</td>
<td>29</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>Severe (%)</td>
<td>27</td>
<td>23</td>
<td>6</td>
</tr>
</tbody>
</table>

aNumber of patients for whom diary card data were available.

The most common adverse events were in the neurological system (48%) followed by the musculoskeletal system (13%) and respiratory system (10%).

DISCUSSION

The patients recruited were attending outpatient departments of hospitals. Their mean age was 39 years, and 91% were women; the majority (73%) had a history of migraine without aura. The demographic and clinical characteristics of the study population were thus typical of the general migraine population.
The results of this study show that 6 mg sumatriptan administered subcutaneously by patients using an auto-injector is an effective and well tolerated treatment for successive attacks of migraine. Sumatriptan was as effective at attack 3 as it was at attack 1, and there was no evidence of an increasing incidence of adverse events with successive uses of the drug.

For each migraine attack treated, about 70% of patients experienced headache relief within 1 h of sumatriptan injection, and at 2 h the level of response had increased to more than 80%. These results are very similar to those found in a placebo-controlled study of the sumatriptan auto-injector used to treat a single migraine attack.12

Many patients with migraine suffer not only headache but also other debilitating symptoms such as nausea, vomiting, photophobia and phonophobia. In the present study the incidence of these symptoms decreased after treatment with sumatriptan (Fig. 2). About 70% of patients who reported nausea, vomiting or photo- or phonophobia before treatment recorded absence of the symptom 2 h after the sumatriptan injection. The relief of such symptoms by subcutaneous sumatriptan has also been demonstrated in previous studies.10–12

Recurrence of headache within 24 h was reported by 20–30% of patients. This level of recurrence is lower than that reported in other studies, in which about 40% of patients injected subcutaneously with sumatriptan reported recurrence of migraine within 24 h10 or 48 h12 of resolution of the initial headache. The reasons for the lower level of recurrence in the present study are not clear. The assessment of recurrence of migraine in clinical trials such as these is difficult. Since in analysing recurrence no account has been taken of the use of rescue medication or of other non-study medication within the intervening period, it is not clear to what extent the rate of recurrence in these studies can be attributed to study medication. A study designed to assess more specifically the issue of recurrence found a recurrence rate within 24 h of 10–15%.16

Sumatriptan has a relatively short plasma half-life of about 2 h,17 and since migraine attacks are often prolonged it may be necessary for some patients to take additional doses to maintain plasma concentrations of sumatriptan over a longer period. A second dose of sumatriptan effectively treated headache recurrence in patients who used it to treat a severe or moderate headache.

Sumatriptan was generally well tolerated. Although about 40% of patients had at least one adverse event, most of the events were assessed as mild or moderate, and were transient. Some adverse events may have been symptoms of the migraine attack itself, rather than reactions to the study drug. The types of events that were observed in the present study were similar to those reported previously.10–12,15

The auto-injector delivers a consistent amount of drug which is readily absorbed, facilitating a rapid response to treatment. Self-injection devices have been used successfully for many years in the treatment of insulin-dependent diabetes.16 Patients reported a high level of satisfaction with the auto-injector treatment of migraine with sumatriptan both in the present study and in the placebo-controlled study reported earlier,12 and they handled the device well.12

Self-administration of sumatriptan using the auto-injector is a highly effective therapy for migraine, particularly in patients with gastro-intestinal symptoms that may impair absorption of the drug.

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References


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APPENDIX

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