Treatment of Acute Migraine With Subcutaneous Sumatriptan

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Sumatriptan succinate, a 5-HT₁₉ receptor agonist, constricts human cranial arteries. Two parallel-group trials for treatment of acute migraines were conducted in the United States. Adult patients were randomized and given either 6 mg of sumatriptan succinate subcutaneously (n = 734) or placebo (n = 370). At 1 hour, sumatriptan was significantly more effective than placebo in reducing moderate or severe headache pain to mild or no pain (70% vs 22%), in completely relieving headache (49% vs 9%), and in improving clinical disability (76% vs 34%). Sumatriptan also reduced nausea and photophobia significantly better than placebo. Patients with residual migraines received another injection; those who had originally received sumatriptan received either a second active injection (n = 167) or placebo (n = 178), while those who had received placebo received a second placebo injection (n = 335). Statistical evidence for benefit of second sumatriptan injection is absent. Adverse events associated with sumatriptan were tingling, dizziness, warm-hot sensations, and injection-site reactions. Sumatriptan is effective and well tolerated in patients with acute migraine.

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EIGHT million Americans have migraines.1 Sufferers often experience two or more incapacitating attacks every month, causing considerable disruption to both work and leisure time.2 β-Blockers, calcium channel antagonists, and antidepressant drugs are sometimes used for prophylaxis. Current therapies for acute migraine include ergot derivatives, analgesics, and antiemetics. The effectiveness of existing rescue treatments for migraines is inconsistent, and the side effects of the treatments may be intolerable.

The pathogenesis of migraine is not well understood. Dilatation of cranial blood vessels is thought to play an important role.3,4 Serotonin (5-HT) is a potent vasoconstrictor and is effective in treating migraines, but its unpleasant side effects prevent its routine use.5

The brain has three classes of 5-HT receptors: 5-HT₁, 5-HT₅, and 5-HT₆. The 5-HT₁ class is further subdivided; stimulation of the 5-HT₁₉ receptors causes vasoconstriction, specifically in the cranial blood vessels in a variety of animal species, including man.6,7 Sumatriptan succinate is a specific 5-HT₁₉ agonist.7 In animals, sumatriptan also blocks plasma extravasation, which may be part of the migraine pathogenesis.8

Sumatriptan has been studied in small, controlled clinical trials by the subcutaneous, intravenous, and oral routes.9,10 We now report the results of two identical, large-scale, multicenter (61 total sites), randomized, double-blind, placebo-controlled studies that show the efficacy and tolerability of sumatriptan in the treatment of patients with acute migraine.

METHODS

Otherwise healthy adults were eligible for enrollment in these studies between May and November 1989. Migraines were diagnosed using a 1-year history of classic migraine (with aura) or common migraine (without aura) and the criteria established by the International Headache Society.11 Written, informed consent was obtained from all patients. The protocol and consent form were approved by an institutional review board for each clinic.

History and results of physical examination, 12-lead electrocardiogram, and routine clinical laboratory tests were recorded at patient screening. Patients with hepatic or renal impairment, history of ischemic heart disease, Raynaud’s disease or syndrome, uncontrolled hypertension, those who had previously been treated with sumatriptan, and those who were pregnant, were using inadequate contraception, or were lactating were excluded.

STUDY DESIGN-PROTOCOL

Patients presenting to the clinic with acute migraines gave information on headaches, concomitant symptoms, and clinical disability. Headaches were verbally rated by patients using a scale from 0 through 3, where 0 indicated no pain; 1, mild pain; 2, moderate pain; and 3, severe pain. Patients had to have moderate (grade 2) or severe (grade 3) headaches in order to be treated. Use of opioids or ergotamine within 24 hours or simple analgesics within 6 hours of study-drug administration disqualified the patient. Long-term prophylactic medications for migraine were not reasons for disqualification.

Qualified patients (n = 1104) were randomly assigned to 6 mg plus 6 mg of sumatriptan succinate, 6 mg of sumatriptan succinate plus placebo, or placebo plus placebo, according to a randomization schedule generated prior to the trial and administered based on the chronological order that patients presented for treatment (Figure 1). Each dose was administered as a 0.5-mL subcutaneous injection over the deltoid muscle of the left or right arm. Absence of pain (grade 0) 1 hour after the first injection disqualified the patient from receiving the second injection. The second dose was given to evaluate whether remediation would provide additional efficacy if the first dose was not effective or if partial relief was achieved. Rescue therapy was administered at the discretion of the investigator if migraine persisted 1 hour after the second dose. Patients could use their usual rescue medications, such as aspirin, acetaminophen, meperidine hydrochloride, and promethazine hydrochloride, but excluding ergotamines.

Efficacy Measurements

Severity of headaches was rated by patients at 10, 20, 30, 40, 50, 60, 90, and...
120 minutes after each dose. Pain relief was prospectively defined as reduction of moderate or severe headache pain (grade 2 or 3) to mild or no headache pain (grade 1 or 0). Mean pain scores and summed pain intensity differences scores are also reported. Patients who received rescue medication were defined as treatment failures.

Clinical disability and presence or absence of nausea, vomiting, and photophobia were assessed on the same schedule as headaches. Clinical disability was rated by patients using the following scale: 0 indicated the ability to work and function normally; 1, working ability mildly impaired; 2, working ability severely impaired; and 3, bed rest required. After discharge and for 48 hours after receiving treatment, patients kept a diary of headaches and of use of rescue medications.

Safety Assessments

Physical examinations and routine clinical laboratory tests were performed before treatment and prior to discharge. Vital signs (heart rate and blood pressure) were measured every 30 minutes after each dose until discharge from the clinic. Adverse events were recorded throughout the in-clinic treatment period and in the diary period.

Statistical Analysis

Nonparametric analyses of pain, clinical disability, nausea, vomiting, and photophobia were used. The last efficacy score prior to rescue medication was carried forward to subsequent time points. The P values were computed for each time point using Mantel-Haenszel and extended Mantel-Haenszel tests. All tests were two-sided, with P<.05 prospectively defined as statistically significant. There was no adjustment of P values to account for multiplicity of testing; reported P values were usually far smaller than those defining statistical significance.

RESULTS

Demographic characteristics and baseline migraine symptoms were comparable between the two studies and among all sites and treatment groups (Table 1). Therefore, the combined results from all patients and both studies are presented herein.

Migraine Relief: First Dose

Sumatriptan provided rapid relief of migraine pain. It was significantly more effective than placebo in treating headache pain at every point from 10 minutes to 1 hour after treatment (P<.001) (Fig 2). At 1 hour, 515 (70%) of 734 patients who had received a single dose of sumatriptan reported mild pain (grade 1) or no pain (grade 0) compared with 81 (22%) of 370 patients who had received placebo (P<.001). Of these, 356 (49%) of 734 patients who had received sumatriptan were completely pain free (grade 0) compared with 35 (9%) of 370 patients who had received placebo (P<.001). Of the 356 patients who were pain free at 1 hour, 351 (99%) were still pain free at 2 hours.

Mean pain scores for patients receiving sumatriptan at 10 minutes were significantly lower than those for patients receiving placebo and remained lower throughout the entire observation period (at 1 hour they were 0.91 vs 2.09; P<.001). The summed pain intensity differences scores at 1 hour were significantly higher in patients receiving sumatriptan compared with placebo (P<.001).

Migraine Relief: Second Dose

Of the 734 patients who initially received sumatriptan, 178 received a sec-
Table 2.—Patients Using Rescue Medications in Placebo and Sumatriptan Succinate Treatment Groups

<table>
<thead>
<tr>
<th>Treatment Groups, No. (%)</th>
<th>Sumatriptan Succinate (n = 734)</th>
<th>Placebo (n = 370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In clinic only</td>
<td>145 (20)†</td>
<td>218 (59)</td>
</tr>
<tr>
<td>Time after treatment, h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>306 (42)†</td>
<td>296 (80)</td>
</tr>
<tr>
<td>16</td>
<td>383 (53)†</td>
<td>313 (85)</td>
</tr>
<tr>
<td>24</td>
<td>445 (61)†</td>
<td>324 (88)</td>
</tr>
<tr>
<td>48</td>
<td>483 (66)†</td>
<td>329 (89)</td>
</tr>
</tbody>
</table>

*Data are combined for two identical trials. Number of patients receiving rescue medication was cumulative throughout the 48-hour period.

**Sumatriptan succinate was significantly better than placebo (P < .001).**

**Rescue Medication**

During the clinic period, 20% of sumatriptan-treated patients received rescue medication compared with 59% of placebo-treated patients (P < .001) (Table 2). However, within 24 hours, 61% of sumatriptan-treated patients and 88% of placebo-treated patients took rescue medication (P < .001). Throughout the diary period, more placebo-treated patients took rescue medications (Table 2).

**Duration of Complete Migraine Pain Relief**

Of the 734 sumatriptan-treated patients, 69% (511/734) were pain free at discharge compared with 22% (80/370) of placebo-treated patients (P < .001). Of the sumatriptan-treated patients, 250 (34%) of 734 remained completely pain free for 24 hours compared with 40 (11%) of 370 of placebo-treated patients. Note that these results are in spite of the greater use of rescue medication by placebo- than sumatriptan-treated patients.

**Safety Results**

Vital sign measurements and clinical laboratory test results were similar before and after treatment for all groups. Seven patients (six sumatriptan-treated and one placebo-treated) withdrew
from the study before receiving a second dose because of adverse events.

One hundred ninety-seven placebo-treated patients (53%) experienced 462 adverse events (1.25 adverse events per patient) compared with 622 sumatriptan-treated patients (85%) who experienced 2275 adverse events (3.1 adverse events per patient). Significantly fewer placebo-treated patients had adverse events that were considered by the investigator to be drug related (156 [79%] of 197 placebo-treated patients compared with 600 [96%] of 622 sumatriptan-treated patients [P < .001]). Adverse events were described as severe in 34 (17%) of 197 placebo-treated patients and in 122 (20%) of 622 sumatriptan-treated patients.

Table 3 shows the specific adverse events occurring at an incidence of 1% or more in the sumatriptan-treated patients. Most adverse events began within minutes of the injection and lasted less than 1 hour.

**COMMENT**

Sumatriptan rapidly reduces the severity and duration of acute migraine. Pain scores analyzed by four methods (mean pain score, percentage of patients achieving a 0 or 1 pain score, percentage of patients who were pain free, and summed pain intensity differences scores) consistently showed sumatriptan to be more effective than placebo in relieving moderate or severe migraines. Sumatriptan also produced significant improvement in clinical disability scores, nausea, and photophobia. A second injection at 1 hour was not associated with significantly more relief of migraine or associated symptoms. A secondary measure of sumatriptan's efficacy was the comparison of rescue medication use between treatment groups. Overall, 88% of placebo-treated patients received rescue medication within 24 hours compared with 61% of sumatriptan-treated patients. This indicates both the need to evaluate the duration of action of a single dose and to define a multiple-dose regimen. However, rescue medications were taken at the patient's discretion. It was not uncommon for patients to self-medicate with rescue medication in anticipation of the return of headache or associated symptoms, in spite of being pain free.

Significantly more adverse events occurred following treatment with sumatriptan than placebo. Concern whether this unblinds the trial must be considered. Since patients were treated only once, which limited their exposure to study medication, and since adverse events and efficacy parameters were reported by the patient, it is unlikely that patients introduced bias into the study results.

In contrast to other migraine trials, the rigorous International Headache Society entry criteria were used to establish the diagnosis of migraine. A simple four-point pain scale has practical advantages, and the data, which were analyzed by four different methods, yielded consistent results. Reproducibility between both studies and among all sites and all four analyses validates this technique.

Most currently available rescue migraine therapies fail to provide consistent pain relief and are associated with potentially intolerable side effects. Simple analgesics are frequently used to treat migraines, often with metoclopramide hydrochloride because of gastric stasis or vomiting during the attack.5,6 Metoclopramide can cause acute dystonic reactions, particularly in young adults.12 Naproxen and aspirin are more effective than placebo in reducing migraines, but the adverse ef-
fects of these nonsteroidal anti-inflammatory drugs are well known.\textsuperscript{38,39} Parenteral narcotics are frequently used in emergency departments, but these may exacerbate the nausea and vomiting seen with migraine and can obscure neurological differential diagnoses. Narcotics also have abuse potential and usually require that the patient remain under observation by the clinician after administration of the drug. Sumatriptan treats headache and migraine-associated nausea, suggesting that concomitant analgesic and antiemetic drugs may be unnecessary.

Ergotamine has been used extensively for many years, although few placebo-controlled studies have demonstrated its superiority to placebo.\textsuperscript{40} Di-hydroergotamine mesylate given intravenously with prochlorperazine edisylate or metoclopramide aborts severe or intractable migraines, although there is a high rate of side effects.\textsuperscript{35} The side effects of ergotamine include nausea and vomiting, tiredness, tingling, chest pain, light-headedness, rebound headache, and peripheral vasoconstriction. In addition, the nonselective vasoconstrictive actions may cause both coronary and peripheral artery spasms, possibly leading to gangrene, angina, and acute myocardial infarction.\textsuperscript{41,42}

The structure of sumatriptan is similar to serotonin, but it is different from the ergot alkaloids. These trials provided no evidence that sumatriptan has the pharmacological actions of ergotamine. This may be due to the selective pharmacological properties of sumatriptan compared with ergotamine.

We conclude that sumatriptan is an effective treatment for patients with acute migraine. A significant reduction in headache, clinical disability, nausea, and photophobia occurs within minutes of a subcutaneous injection, with lasting effects for up to 24 hours.

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References


