

Oral Sumatriptan in the Treatment of Recurrent Headache

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Background: Sumatriptan is effective for the treatment of acute migraine. However, headache may recur in about 30% of patients within 24 hours of successful treatment.

Objective: To evaluate the efficacy of oral sumatriptan, 100 mg, in the treatment of headache recurring within 24 hours of achieving headache resolution with subcutaneous sumatriptan, 6 mg.

Study Design: Subcutaneous sumatriptan was administered for up to 12 migraine attacks in a randomized, double-blind, parallel-group study. Patients whose headache was completely resolved 90 minutes after subcutaneous dosing received either oral sumatriptan or placebo at the onset of recurrent headache. Patients whose headache was not completely resolved were offered rescue medication, including sumatriptan. Patients rated headache severity for 24 hours.

Setting: Fifteen US outpatient clinics.

Main Outcome Measure: Percentage of patients

with relief of recurrent headache and adverse events.

Results: Approximately 90% of patients achieved relief of headache (severe or moderate headache reduced to mild or no headache) by 90 minutes after unblinded subcutaneous administration of sumatriptan. Efficacy rates were at least 80% regardless of whether the headache fulfilled the International Headache Society criteria for migraine. About 64% of patients achieved complete relief. Oral sumatriptan, 100 mg, relieved moderate or severe recurrent headache within 4 hours in up to 81% of patients. Oral sumatriptan administered as rescue medication to patients not headache-free did not relieve persistent headache. The incidence, pattern, and severity of adverse events after combined subcutaneous and oral administration of sumatriptan were similar to those after subcutaneous administration alone.

Conclusions: Oral sumatriptan was consistently effective in the treatment of headache recurrence.

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P RIMARY CARE physicians are frequently consulted for migraine,¹ which afflicts at least four of every 100 Americans.²

Results of recent studies demonstrate that migraine is associated with substantial personal debilitation as well as large costs to society.³⁻⁵ For example, in a recent survey administered to 158 migraineurs, about 85% reported that migraine prevented them from functioning normally some or most of the time.⁶ Both men and women said that migraine had caused them to miss at least 1 day of work in the preceding month, and over one third of respon-

dents reported that migraine always reduced their effectiveness at work.

Until recently, a single medication effective for the majority of migraine patients was not available. Sumatriptan, a new drug for the treatment of migraine, alleviates headache and associated migraine symptoms, such as nausea, vomiting, photophobia, and phonophobia, in over 80% of patients within 120 minutes

See Methods on next page

From the Shealy Institute, Springfield, Mo.

METHODS

SUBJECTS

Four hundred twenty-four men and women aged 18 to 72 years with a diagnosis of migraine were enrolled. Pregnant or lactating women were excluded. Patients with a history of ischemic heart disease, Prinzmetal's angina, or Raynaud's syndrome or with diastolic or systolic blood pressure greater than 95 or 160 mm Hg, respectively, were also excluded. All patients gave written informed consent.

DESIGN AND PROCEDURE

The protocol for this randomized, double-blind, parallel-group study (**Figure 1**) was approved by an institutional review board for each of the 15 sites. Over a period of 1 year, each patient could use subcutaneous sumatriptan, 6 mg, in the clinic setting to treat up to 12 attacks that were determined by the clinician to be migraine. Whether or not the clinician used IHS diagnostic criteria was left to his or her discretion. For any particular attack, patients who used an analgesic or antiemetic agent within 4 hours of treatment with sumatriptan or patients who had been free of headache for fewer than 24 hours since the last treatment with the study drug were excluded. Patients used a four-point scale to rate their headache severity immediately before and 30, 60, and 90 minutes after subcutaneous treatment with sumatriptan:

Headache Severity	Grade
None	0
Mild	1
Moderate	2
Severe	3

Immediately before and 30, 60, and 90 minutes after subcutaneous dosing, patients also rated nausea, vomiting, photophobia, and phonophobia as present or absent. In addition, clinical disability was rated on a four-point scale, with 0 indicating able to work/function normally; 1, working ability impaired to some degree; 2, severely impaired working ability; and 3, requires bed rest.

Responders to subcutaneous sumatriptan (patients completely free of headache 90 minutes after subcutaneous treatment with sumatriptan) were discharged from the clinic at least 90 minutes after treatment. Before discharge, they were randomly given either oral sumatriptan, 100 mg, or placebo to take at home in the event of headache recurrence, which was defined as return of mild, moderate, or severe headache within 24 hours of dosing with subcutaneous sumatriptan. After the first attack to which they responded, responders to subcutaneous sumatriptan were randomized to receive either oral sumatriptan, 100 mg, or placebo for every recurrence. Responders used the four-point scale to rate the severity of recurrence on diary cards every 2 hours for 24 hours after oral dosing.

Nonresponders to subcutaneous sumatriptan (pa-

tients with mild, moderate, or severe headache 90 minutes after treatment) could receive rescue medication, including a single 100-mg dose of sumatriptan. Nonresponders rated their headache severity on diary cards every 2 hours for 24 hours after the use of rescue medication or after the initial 90-minute assessment if no rescue medication was taken. The choice of rescue medication was left to the discretion of the investigator, but ergotamine agents were excluded. Nonresponders who took rescue medication were considered treatment failures, and that migraine attack was excluded from further evaluations.

For both responders and nonresponders, the occurrence of adverse events (any untoward medical occurrence, drug related or not) was recorded throughout the in-clinic phase by the investigator and for the remainder of the study on diary cards. Vital signs were assessed before each drug treatment and at the end of each 90-minute postdose interval. Changes in vital signs deemed "clinically significant" included the following: systolic blood pressure of 180 mm Hg or greater with an increase of 20 mm Hg or greater, or 90 mm Hg or less with a decrease of 20 mm Hg or greater; diastolic blood pressure of 105 mm Hg or greater with an increase of 15 mm Hg or greater or 50 mm Hg or less with a decrease of 15 mm Hg or greater; or heart rate of 120 beats per minute with an increase of 15 beats per minute or greater, or 50 beats per minute or less with a decrease of 15 beats per minute or greater. Clinical laboratory tests were performed quarterly. Patients were dropped from the study if they had a serum creatinine concentration of 160 $\mu\text{mol/L}$ (1.8 mg/dL) or greater or if they had alanine aminotransferase or aspartate aminotransferase concentrations more than two times above normal levels.

DATA ANALYSES

The primary efficacy measure was the percentage of responders (no headache at 90 minutes) whose moderate or severe recurrent headache (score of 2 or 3) was reduced to mild or no headache (score of 1 or 0) 2 or 4 hours after oral dosing. The percentage of responders whose mild recurrent headache (score of 1) was reduced to no headache (score of 0) was also assessed. Other measures included the percentage of nonresponders who achieved headache relief (score of 0 or 1) after using oral sumatriptan as rescue medication and the efficacy of subcutaneous sumatriptan at alleviating headache and associated symptoms in patients with migraines that were or were not diagnosed according to IHS criteria.

The significance level for all statistical tests was prospectively set at $P < .05$. Between-group differences in the percentage of patients with particular headache severity and clinical disability scores were tested for each attack with the van Elteren test. Between-group differences in the percentage of patients with and without nausea, vomiting, photophobia, and phonophobia were tested for each attack with the Cochran-Mantel-Haenszel test. The safety measures were the percentage of patients with potentially drug-related adverse events and the occurrence of abnormalities on clinical laboratory tests.

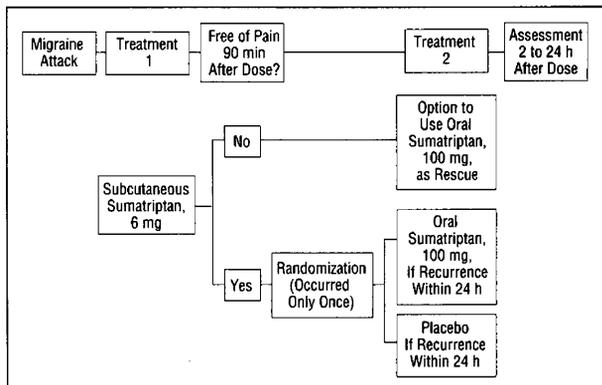


Figure 1. Study protocol.

of subcutaneous administration.⁷⁻⁹ An oral formulation is comparably effective within 4 hours.^{10,11} (At the time of this report, Food and Drug Administration approval for oral sumatriptan, which had not yet been marketed in the United States, was pending.)

Over 50% of patients experience complete relief of their migraine episode after a single oral or subcutaneous dose of sumatriptan. However, headache may recur in about 30% of patients within 24 hours after initial resolution of symptoms.^{7,11} That these symptoms represent a recurrence rather than a new attack is supported by the observations that headache recurs and resolves within the typical 4- to 72-hour duration of a migraine attack and that aura and other preheadache or premigraine phenomena do not recur.¹² The mechanism of recurrent headache in migraine has not been determined, although the short half-life of sumatriptan (approximately 2 hours) relative to the usual duration of a migraine attack may be a contributing factor.¹² Recurrence also occurs after successful treatment of headache with other drugs, such as aspirin combined with metoclopramide¹¹ or ergotamine.^{12,13}

This study was conducted to evaluate (1) the efficacy of oral sumatriptan, 100 mg, in the treatment of headache recurring within 24 hours after patients have achieved complete headache relief with subcutaneous sumatriptan, (2) the efficacy of oral sumatriptan as a rescue medication in patients whose headache did not resolve with subcutaneous sumatriptan, and (3) the efficacy of subcutaneous sumatriptan in migraines that fulfilled the diagnostic criteria of the International Headache Society (IHS)^{14,15} compared with headaches that did not fulfill the IHS criteria.

RESULTS

PATIENT CHARACTERISTICS

Four hundred twenty-four patients enrolled in the study and received subcutaneous sumatriptan at least once (Table 1). Demographic characteristics were similar be-

Table 1. Patient Characteristics

	Placebo for Recurrence	Oral Sumatriptan for Recurrence
No. of patients	211	213
Mean age, y	40.3	42.0
Sex, No. (%)		
M	19 (9)	30 (14)
F	192 (91)	183 (86)
Race, No. (%)		
W	197 (93)	196 (92)
B	6 (3)	13 (6)
Other	8 (4)	4 (2)
Patients dropped from study, No.		
Adverse events	10	10
Lack of efficacy	6	15
Treatment failure*	43	35
Pregnancy	4	1
Protocol violation	11	16
Headache type, % of attacks†		
IHS migraine without aura	71	72
IHS migraine with aura	9	7
IHS episodic tension-type	3	5
IHS chronic tension-type	<1	0
IHS cluster headache	<1	0
Non-IHS headache	16	16

*Patients who took a rescue medication prior to achieving relief with subcutaneous sumatriptan.

†Headache types in this table are based on a computer algorithm analysis of symptoms that led to diagnosis. All headaches treated with subcutaneous sumatriptan in this study were diagnosed as migraine by a clinician, although the computer did not diagnose all of these headaches as migraine. IHS indicates International Headache Society.

tween groups. Of the 1904 attacks that were treated, 16% did not fulfill IHS migraine criteria.

One hundred fifty-one patients were dropped from the study before it was terminated (Table 1). In 246 of the 424 enrolled patients, at least one recurrence was treated with oral sumatriptan or placebo, and in 160, 107, and 75 patients, respectively, two, three, and four recurrences were treated. Too few patients were treated for five or more recurrences to make statistical comparisons involving efficacy data.

EFFICACY OF SUBCUTANEOUS SUMATRIPTAN

Predose headache severity was scored as 1, 2, or 3 (mild, moderate, or severe) for all patients to whom subcutaneous sumatriptan was administered. A total of 1904 attacks were treated. Eighty-nine percent of all patients achieved headache relief (score reduced to 0 or 1) by 90 minutes after dosing with unblinded subcutaneous sumatriptan (Table 2); 64% of patients achieved complete relief (score of 0). Efficacy rates were at least 80% regardless of whether the migraine was diagnosed according to IHS criteria. Sumatriptan was similarly effec-

Table 2. Efficacy of Subcutaneous Sumatriptan, 6 mg, for Initial Migraine in up to 12 Attacks

	% of Patients	
	Predose	90 Minutes After Dose
Overall relief*	11†	89
Free of pain	0	64
Overall relief by headache type‡		
IHS migraine without aura	...	90
IHS migraine with aura	...	86
IHS episodic tension-type	...	99
Non-IHS headache	...	80
No clinical disability	3	68
Nausea	75	11
Phonophobia	78	14
Photophobia	92	24
Vomiting	8	1

*A reduction in score from 3 or 2 to 1 or 0 or a reduction in score from 1 to 0.

†Mild pain only (score of 1) before dosing.

‡IHS indicates International Headache Society.

tive at alleviating nausea, vomiting, photophobia, and phonophobia and at restoring patients to normal function.

CHARACTERISTICS OF RECURRENT HEADACHE

Recurrences occurred in 725 of the 1221 attacks successfully treated with subcutaneous sumatriptan. For patients who were treated in one to four attacks, the incidence rates of recurrence after every attack were 54%, 36%, 29%, and 17%, respectively. Data from patients who were treated in one to 12 attacks indicate that as the number of treated migraines increased, the number of patients with recurrences after every attack decreased. Overall, 34% of responders to subcutaneous sumatriptan had recurrent headache after every attack for which they were treated (regardless of the number of attacks that were treated). A review of data from all recurrences showed that trends in the data for the fifth through the 12th recurrences were similar to those for the first through the fourth recurrences.

The severity of recurrent headache for the first, second, third, and fourth recurrences was mild in 50%, 47%, 46%, and 54% of all responders, respectively, and moderate in 42%, 42%, 44%, and 39% of responders, respectively. Only 9%, 13%, 11%, and 8% of responders, respectively, experienced severe recurrent headache for the first, second, third, and fourth recurrences. The median time to recurrence (time from subcutaneous treatment to return of migraine) was 8.8 hours. The median time to recurrence ranged from 7.9 to 11.3 hours in the oral placebo group and from 8.2 to 10.8 hours in the oral sumatriptan group.

EFFICACY OF ORAL SUMATRIPTAN IN RECURRENT MIGRAINE

Two hours after oral dosing for the first through the fourth recurrences, relief (recurrent headache score reduced from 2 or 3 to 0 or 1) was experienced by 67% to 69% of sumatriptan-treated patients compared with 17% to 29% of placebo-treated patients (**Figure 2**; $P \leq .005$ for each recurrence). Four hours after oral dosing for the first through the fourth recurrences, relief was experienced by 71% to 81% of sumatriptan-treated patients compared with 17% to 27% of placebo-treated patients ($P \leq .001$ for each recurrence). Among patients with mild recurrent headache (score of 1), 2 hours after oral dosing, 46% to 56% of sumatriptan-treated patients compared with 6% to 15% of placebo-treated patients achieved a score of 0 ($P \leq .008$ for each recurrence). Four hours after oral dosing, 52% to 73% of sumatriptan-treated patients compared with 19% to 22% of placebo-treated patients achieved a score of 0 ($P \leq .001$ for the first, second, and third recurrences; $P = .057$ for the fourth recurrence).

The median time to relief after oral sumatriptan was 2.0 hours, and the median time to complete relief (score of 0) ranged from 2.4 to 4.2 hours. Thirty-seven percent to 46% of patients treated with oral sumatriptan compared with 11% to 20% of patients treated with placebo maintained relief for 24 hours after oral dosing.

EFFICACY OF ORAL SUMATRIPTAN IN PATIENTS WHOSE HEADACHE DID NOT RESPOND TO SUBCUTANEOUS SUMATRIPTAN

In patients whose headache failed to respond to the initial subcutaneous dose, oral sumatriptan taken as rescue medication also failed. Eighty percent (80%) of patients who were not free of headache 90 minutes after subcutaneous sumatriptan had mild headache (score of 1) before they took oral sumatriptan as rescue medication. From 2 to 24 hours after the use of oral sumatriptan as rescue medication, the percentage of nonresponders with mild or no headache decreased, a finding that reflects the lack of efficacy of the 100-mg tablet as rescue medication. From 2 to 24 hours after the use of oral sumatriptan as rescue medication, an increasing percentage of nonresponders took additional rescue medication, which disqualified them from further analyses.

SAFETY OF SUMATRIPTAN

Data from all treated attacks (≤ 12) were included in the safety analyses. The percentage of patients with adverse events was similar in the groups treated with subcutaneous sumatriptan followed by oral sumatriptan or placebo. **Table 3** shows adverse events that occurred in at least 5% of patients treated with sumatriptan for up to

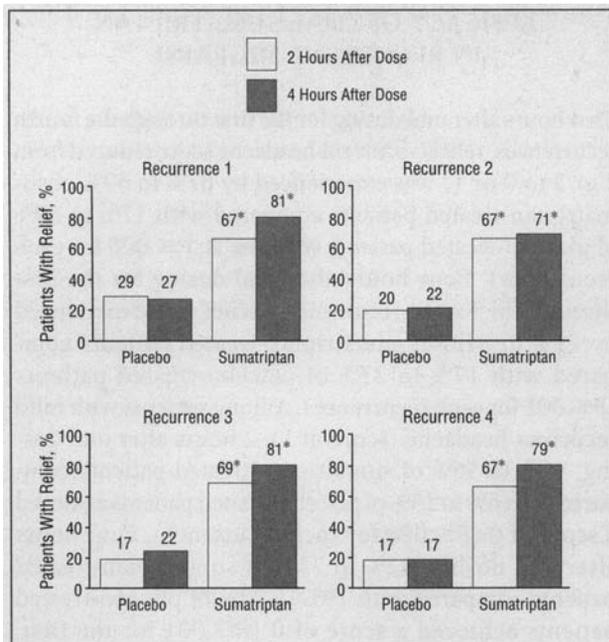


Figure 2. Percentage of patients whose recurrent migraine (pain score of 3 or 2) was relieved (pain score of 0 or 1) 2 and 4 hours after treatment with oral sumatriptan, 100 mg, or placebo, for the first through fourth recurrences. Asterisk indicates $P < .0005$.

12 attacks. The most frequently reported adverse events were injection site reaction, nausea and/or vomiting, and tingling.

The data tabulated according to the number of treated attacks with adverse events were similar to the data tabulated according to the number of patients with adverse events. Adverse events that occurred in at least 5% of treated attacks included (percentages for the placebo group and the oral sumatriptan group, respectively) injection site reaction (35% and 29%), nausea and/or vomiting (9% and 11%), feeling of heaviness (5% and 7%), warm/hot sensation (7% and 4%), chest symptoms (5% and 5%), pressure sensation (5% and 5%), burning sensation (5% and 5%), and flushing (5% and 4%).

Twenty patients were withdrawn from the study because of adverse events, including one or more of the following: abnormal (according to predefined criteria) liver function test results, six patients; pain, pressure, or strange feeling in the chest, five patients; burning (including injection site), tingling, and/or numbness, four patients; nausea and/or vomiting, two patients; headache, two patients; neck spasm, one patient; change in vital signs, one patient; rash, one patient; polyarthritis, one patient; uterine hemorrhage, one patient; and angioma, one patient. All events that were considered related or possibly related to administration of the study drug resolved spontaneously, most within a few minutes of onset.

Four patients experienced cardiovascular events that warranted special attention. One 35-year-old woman had a diagnosis of cerebellar venous angioma (not considered to be drug related) that led to her being dropped

Table 3. Patients With Specific Adverse Events (All Attacks Combined)*

Adverse Event	% of Patients	
	Placebo for Recurrence (n=306 Attacks)	Oral Sumatriptan for Recurrence (n=304 Attacks)
Any adverse event	83	84
Injection site reaction	51	49
Nausea and/or vomiting	20	25
Tingling	20	15
Migraine	8	16
Feeling of heaviness	10	13
Warm/hot sensation	15	9
Pressure sensation	10	11
Burning sensation	11	10
Chest symptoms	11	10
Flushing	10	10
Neck pain/stiffness	8	10
Disorders of mouth/tongue	9	7
Dizziness/vertigo	7	9
Feeling strange	6	5
Numbness	6	5
Feeling of tightness	5	6
Disturbance in nasal cavity/sinuses	5	6
Myalgia	5	4
Drowsiness/sedation	5	4
Sweating	6	3

* Adverse events that occurred in either treatment group with an incidence of 5% or more are reported. Patients may have been treated for up to 12 migraine attacks.

from the study. A second woman aged 66 years developed chest pain, left arm numbness, diaphoresis, and decreases in blood pressure and heart rate 4 minutes after treatment with subcutaneous sumatriptan, 6 mg. An electrocardiogram obtained approximately 35 minutes after the dose revealed ST segment and T-wave elevation in leads V_1 to V_3 , changes that resolved 3 minutes after treatment with one sublingual nitroglycerin tablet. Serial electrocardiograms and cardiac enzyme tests for 24 hours after this event revealed no evidence of ischemia or

Twenty patients were withdrawn from the study because of adverse events

myocardial infarction. The patient was withdrawn from the study, and results of follow-up stress tests and Holter monitoring during a migraine-free period were normal. A third patient reported nausea and palpitations 25 minutes after dosing with subcutaneous sumatriptan, 6 mg. Forty minutes later, both events spontaneously resolved, and the patient chose to withdraw from the study because of the nausea. Finally, one patient with a pre-dose electrocardiogram suggesting a possible anterolateral infarct received subcutaneous sumatriptan, 6 mg, for

one migraine attack. He experienced arm numbness and cold sensations in the extremities shortly after dosing. No chest discomfort was noted. Both events resolved spontaneously, and no further action was needed.

Eight patients experienced clinically significant changes (from predefined criteria) in vital signs at some time during the study. Seven of these patients experienced isolated, transient decreases in systolic blood pressure, and the remaining patient experienced a decrease in heart rate. No patient experienced adverse events symptomatic of vital sign abnormalities, and none of the eight patients with clinically significant changes in vital signs was withdrawn from the study as a result.

Twenty-four patients had clinically significant abnormalities in clinical laboratory test results at some time during the study. Fourteen of these 24 patients had hematologic abnormalities attributed to allergic or infectious disease. The remaining 10 patients had liver function test abnormalities, although none had clinical signs or symptoms characteristic of liver impairment. All abnormal liver function test results except one were considered unrelated to the study drug; some were attributed to the use of alcohol or other drugs. One patient with a nondisqualifying elevated baseline alanine aminotransferase level also had elevated alanine aminotransferase levels at various times during treatment. The investigator considered the alanine aminotransferase elevations possibly related to treatment with the study drug, although the use of alcohol was also listed as a possible contributing factor.

COMMENT

The results of this study demonstrate that oral sumatriptan, 100 mg, is an effective treatment for headache recurring within 24 hours of initial resolution of headache treated with subcutaneous sumatriptan, 6 mg. For the first through the fourth recurrences, headache was relieved in up to 81% of patients treated with oral sumatriptan compared with 17% to 27% of patients treated with placebo. About half of the patients treated with oral sumatriptan maintained relief for 24 hours. Similar efficacy rates were observed regardless of the number of recurrences that were treated. The onset of relief of recurrent headache occurred by 2 hours after dosing, and complete relief was achieved by 4 hours after dosing. These values are consistent with those observed with oral sumatriptan administered for initial (nonrecurrent) migraine.^{10,11}

Data from this study describing the characteristics of recurrent headache also corroborate others' findings. In the present study, up to 43% of responders with moderate or severe headache before treatment with subcutaneous sumatriptan experienced a return of moderate or severe headache within 24 hours of subcutaneous dosing. Similarly, the Subcutaneous Sumatriptan Interna-

tional Study Group⁷ reported that 34% to 38% of patients with moderate or severe headache before treatment with subcutaneous sumatriptan, 6 or 8 mg, experienced a return of mild, moderate, or severe headache within 24 hours. The median time to recurrence was approximately 13 hours (interquartile range, 6.8 to 19.9 hours) after a single subcutaneous dose of sumatriptan, 6 mg, compared with about 9 hours in the present report.

Thirty-four percent of patients had recurrent headache after every treated attack. The rate of recurrence after every attack decreased as the number of treated attacks increased. About 50% of patients experienced recurrence after the first attack treated with subcutaneous sumatriptan. By the fourth attack, only 17% of patients had consistently experienced a recurrence after every treated attack. These data suggest that there is not a type of patient likely to suffer recurrent migraine. Rather, recurrence occurs inconsistently and unpredictably.

The onset of relief of recurrent headache occurred by 2 hours after dosing, and complete relief was achieved by 4 hours after dosing

Sumatriptan was effective for initial as well as recurrent headache in this study. Relief of initial headache and other symptoms was achieved in 88% to 90% of patients treated with subcutaneous sumatriptan compared with 10% to 11% of patients treated with placebo. Similarly high efficacy rates have been reported by others.⁷⁻⁹ In the present study, efficacy rates were about the same whether or not the headache fulfilled IHS criteria for migraine (Table 2). Although these rigorous criteria have been shown to have a high degree of specificity, they are regarded by some clinicians as overly restrictive, a point of view supported by the present study.¹ The data suggest that within this migraine population, a broad spectrum of headaches respond to sumatriptan regardless of whether the headaches adhere to IHS criteria.

In patients whose initial response to sumatriptan was insufficient, a subsequent dose of oral sumatriptan did not provide relief of persistent headache. These data confirm those in a study by R.K.C. and colleagues,⁸ who found that headache was not relieved by a second dose of subcutaneous sumatriptan, 6 mg, administered 1 hour after the first dose to patients whose headache failed to respond to the first dose. A second dose of sumatriptan was also administered 1 hour after the first injection to patients not completely free of headache after the first injection in the Subcutaneous Sumatriptan International Study Group.⁸ In that study, the degree of efficacy of two 6-mg injections of sumatriptan was about the same as that of a 6-mg injection followed by placebo. The results of

these three studies suggest that in patients who do not respond to initial sumatriptan administration, residual headache is not alleviated by additional doses of sumatriptan.

Like the efficacy data, the safety data from this study are consistent with previously reported findings.⁷⁻¹¹ The incidence, pattern, and severity of adverse events after combined subcutaneous and oral administration were similar to those after subcutaneous administration alone. The most frequently reported adverse events following subcutaneous and oral administration of sumatriptan were injection site reaction, nausea and/or vomiting, tingling, and flushing. Most adverse events were transient, and they resolved without medical treatment.

Taken together, these results indicate that oral sumatriptan, 100 mg, relieves headache recurring within 24 hours after initial resolution of headache with subcutaneous sumatriptan, 6 mg. The use of oral sumatriptan within 24 hours of subcutaneous sumatriptan administration appears to be as well tolerated as administration of the subcutaneous formulation alone.

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