Efficacy, Safety, and Tolerability of Oral Eletriptan for Treatment of Acute Migraine: A Multicenter, Double-Blind, Placebo-Controlled Study Conducted in the United States

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Objective.—To investigate the efficacy, consistency, safety, and tolerability of oral eletriptan in the acute treatment of three migraine attacks.

Background.—Eletriptan is a selective 5-$HT_{1B/1D}$ agonist member of a class of agents known to be effective in the acute treatment of migraine.

Methods.—Thirteen hundred thirty-four patients were randomized to 20 mg, 40 mg, or 80 mg of eletriptan, or placebo and could treat up to three attacks. The primary efficacy endpoint was 2-hour headache response for the first attack. Secondary endpoints included associated symptom relief, and pain-free, sustained pain-free, and consistency of response.

Results.—Eletriptan 20 mg, 40 mg, and 80 mg achieved significantly ($P < .0001$) better headache response rates than placebo at 2 hours (47%, 62%, and 59%, respectively, versus 22%) and 4 hours (64%, 76%, and 79%, respectively, versus 25%). Headache response was observed to be rapid, showing improvement at 0.5 hour and 1 hour. Two-hour pain-free response rates for eletriptan 20 mg, 40 mg, and 80 mg were 14%, 27%, and 27%, respectively, compared with 4% for placebo. Sustained pain-free response rates were significantly ($P < .001$) better for eletriptan 20 mg (10%), 40 mg (20%), and 80 mg (18%) compared with placebo (3%). Eletriptan had a higher consistency of intrapatient response than placebo in two of three (68% to 82%) and three of three attacks (32% to 60%) versus 16% and 8%, respectively. All eletriptan doses yielded significant functional improvement at 2 hours. Adverse events were generally mild or moderate and transient, with eletriptan 20 mg having an adverse event profile comparable to placebo.

Conclusions.—Eletriptan is efficacious, displaying high consistency of response over multiple attacks, and is well tolerated for the acute treatment of migraine.

Key words: eletriptan, migraine, consistency of response, functional impairment, triptan

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The currently marketed triptans are selective 5-hydroxytryptamine$_{1B/1D}$ (5-$HT_{1B/1D}$) agonists that have shown excellent efficacy in the treatment of acute migraine.[1] Their antimigraine action is believed to be due to selective vasoconstriction of dilated extracerebral intracranial blood vessels. Other known physiologic effects of triptans may also play a role in migraine relief: these include reduction in neuropeptide release and plasma protein extravasation across dural vessels, and inhibition of nociceptive impulse transmission within the central nervous system.[2]

Eletriptan is a triptan with pharmacokinetic properties that might be expected to give improved clinical efficacy over other triptans. It is more rapidly absorbed following oral administration and it shows

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linear pharmacokinetics following both oral and intravenous administration.[3] Eletriptan has a 4- to 8-fold higher affinity than sumatriptan for the 5-HT_{1B} and 5-HT_{1D} receptors yet still has a low affinity for other 5-HT receptor subtypes.[4] In preclinical and ex vivo models, this has been shown to result in relatively high vasoconstrictor activity for meningeal arteries but a minor effect on other arteries, including femoral and coronary arteries,[5,6] however, this has not yet been conclusively linked to greater clinical safety in patients with coronary heart disease and should not be interpreted as such.

Four, multinational, phase III, placebo-controlled, comparison studies have previously shown that eletriptan (at 20, 40, and 80 mg) is safe and effective in the acute treatment of migraine and is a promising addition to the clinical armamentarium.[7-10] All four studies were conducted at investigational centers outside of the United States. This study aimed to confirm the clinical performance of eletriptan in US patients. The specific objectives were to further investigate the efficacy, safety, and tolerability of three dose levels (20, 40, and 80 mg) of oral eletriptan in the acute treatment of migraine attacks, and to examine the consistency of effect across three attacks.

METHODS

Patients.—The study population consisted of men and women over 18 years of age enrolled at 48 study sites in the United States. Patients had a history of at least one typical attack of migraine with or without aura every 6 weeks, as defined by the International Headache Society (IHS) criteria.[11] Patients also had to be capable of taking study medication as outpatients and recording its effects.

Patients who had previously taken oral eletriptan were excluded from the trial, as were patients who had taken any investigational drug within the previous month. Potentially fertile, sexually active women not using adequate contraception were excluded from the trial, as were women who were pregnant or breast-feeding. Patients with frequent nonmigrainous headache, atypical migraine that had not consistently responded to therapy, migraine with prolonged aura, familial hemiplegic migraine, basilar migraine, or migrainous infarction were excluded from the trial. Patients with a history of heart disease, hypertension or arrhythmias, clinically significant abnormalities in laboratory tests or an electrocardiogram (ECG), documented allergic reactions to drugs, or any other clinically significant disease were also excluded. Written informed consent was obtained from all patients, and the study was approved by appropriate institutional review boards prior to implementation. The study was conducted in compliance with ethical principles in accordance with the Declaration of Helsinki, 1989.

Study Design.—This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in which patients treated up to three attacks of migraine headache. Treatment groups were eletriptan 20 mg, 40 mg, and 80 mg, or placebo. A medical history was taken from each patient; each received a physical examination and was given a migraine diary and medication for the first attack. Eletriptan and placebo were supplied as oral tablets that were identical in appearance. The drug blinding code was sealed and only able to be broken in case of a medical emergency. Random assignment to study treatment group was made based on a computer-generated random number code.

Patients were instructed to take a dose of study medication within 6 hours of onset of a migraine attack, provided that: the headache was moderate to severe in intensity and was not improving; no other analgesic or antiemetic had been taken in the previous 6 hours; no sumatriptan, ergotamine, or similar agent had been taken in the previous 48 hours; and any aura phase had ended. Patients recorded their symptoms in the diary immediately predose, at 30 minutes, and at 1, 2, 4, 6, and 24 hours after taking the study medication.

Patients whose headache did not respond to treatment, or who had a recurrence, were permitted to take a second, blinded, randomized dose of either eletriptan or placebo once 4 hours had elapsed since the first dose. Data on the response to this second dose were analyzed in a separate prospectively planned meta-analysis.[12] Patients with no response after a second dose of study medication were permitted to take rescue medication 2 hours after the second dose. Triptans, ergotamine, or ergotamine-related compounds were not permitted as rescue medication.

Patients returned for a clinic visit within 7 days of the first attack and were provided with study medication and diaries for the next two attacks. They received the same double-blind medication that they had received for the first attack. Patients returned for a final clinic visit at 3 months after the baseline physical examination or within 7 days of treating a third migraine attack, whichever occurred first.

The primary endpoint of this study was the headache response at 2 hours after treatment for the first attack. Secondary endpoints included headache, pain-free response, and functional response at 30 minutes and 1, 2, 4, 6, and 24 hours after treatment; headache recurrence within 24 hours of successful treatment use of rescue medication; relief of migraine-associated symptoms (photophobia, phonophobia, nausea, and vomiting); overall patient acceptability; and consistency of headache response at 2 hours across all three attacks for those patients who treated three attacks. In addition, a post hoc analysis was conducted of sustained response and sustained pain-free response (headache or pain-free response at 2 hours with no recurrence and no use of rescue medication for 24 hours).

The severity of head pain was assessed on a 4-point scale: from 0 (pain absent) to 1 (mild pain), 2 (moderate pain), and 3 (severe pain). A headache response was defined as an improvement in headache severity from grade 2 or 3 at baseline to grade 0 or 1 after treatment. A recurrent headache was defined as showing a response within 2 hours of treatment, followed by worsening to grade 2 or 3 within 24 hours of treatment.

The functional impairment of daily activities was assessed on a 4-point scale as 0 (normal function in spite of headache), 1 (reduced activity), 2 (severely reduced activity), or 3 (bed rest). A functional response was defined as an improvement from grade 2 or 3 at baseline to grade 0 or 1 after treatment. Nausea was assessed on a 4-point scale: 0 (none), 1 (mild), 2 (moderate), or 3 (severe); however, to simplify, presentation is described as present or absent. Photophobia, phonophobia, and vomiting were each recorded as present or absent.

The subjective acceptability of treatment was assessed by asking patients the question, "Given the choice between this and any other medication to treat a migraine attack, would you take this again?" The question was asked 24 hours after taking the second dose (or 24 hours after the first dose if only one dose was taken).

Safety and Laboratory Tests.—The medical examination on study entry included pulse rate and blood pressure measurements, routine laboratory measurements of hematology and clinical chemistry, and a 12-lead ECG. These tests were repeated when patients visited the clinic 1 to 7 days after the first and third attacks. Patients attended the clinic 3 months after the baseline visit if a third attack had not been treated during the study.

Twenty-four hours after taking study treatment, patients were given a diary reminder to record information on any adverse events they had experienced (regardless of their apparent relationship to study medication) and any concomitant medication they had taken.

Statistical Methods.—Sample sizes for the study were chosen in order to give an 80% power to detect a 50% response at the primary endpoint in the eletriptan groups. Two-hour response rates in a previous study were approximately 50% for eletriptan and 35% for placebo.[13] A minimum sample size of 182 patients per group was obtained using the Pfizer program, SAMSIZ, based on the sample-size formula derived by Casagrande et al.[14] However, in order to have sufficient numbers of patients for: (1) analysis of secondary endpoints, and (2) prospectively planned meta-analysis of the effects of a second dose of eletriptan, a larger sample size of 300 patients per group was chosen. All analyses were performed on the intent-to-treat (ITT) population, which included all patients with baseline and on-treatment data. The primary efficacy endpoint, headache response at 2 hours posttreatment, was analyzed using a logistic regression model to fit a dose response to the data. The variables used were the headache responder rate, treated as a binary variable (response/no response); the dose received in milligrams, treated as a continuous variable with placebo having a value of zero; and baseline headache severity as a binary variable (moderate/severe). Analysis of covariance was used to compare each eletriptan group with the placebo group. A step-down procedure was used to make comparisons

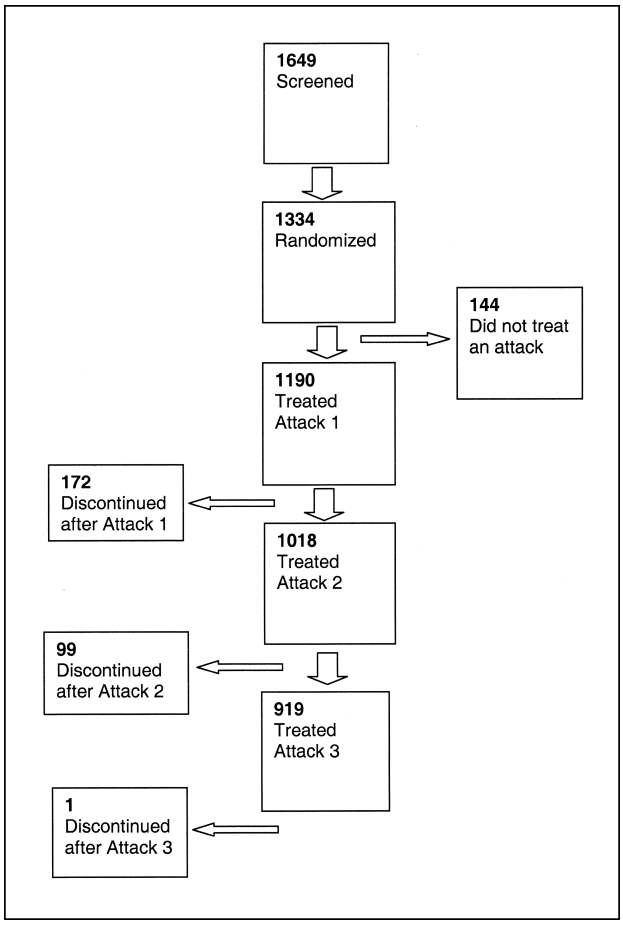

Fig 1.—Patient disposition. Discontinuations were primarily due to no headache during 3-month study period. Other reasons were lost to follow-up and protocol violation.

between treatment groups. The first comparison made was between the eletriptan 80-mg group and the placebo group. If this was significant at least at the two-sided 5% level, the comparison between the eletriptan 40-mg group and placebo was performed. If this second test was significant, then a third comparison was performed between the eletriptan 20-mg group and the placebo group. No formal comparisons were made between eletriptan dose groups. Data for secondary endpoints were analyzed using the same methods.

RESULTS

Patients.—The disposition of patients in the study is shown in Figure 1. Thirteen hundred thirty-four patients were randomized to the 4 study groups, of whom 1190 were treated for the first attack. The most common reason for discontinuation was that the patient did not experience or treat an eligible migraine attack within the 3 months allowed for the trial.

There were no substantial differences between treatment groups with regard to sex, age, race, migraine characteristics, or previous sumatriptan experience (Table 1). Patients were predominantly women and white. Mean age of the patients in the study was 42 years. Over 60% of patients in each group had previously used sumatriptan. Patients had suffered a mean of nine migraine attacks in the previous 3 months.

Table 1.—Study Population Characteristics

Feature	Eletriptan 20 mg (n = 290)	Eletriptan 40 mg (n = 296)	Eletriptan 80 mg (n = 312)	Placebo (n = 292)
Sex, female, %	85	85	90	88
Age, mean (range), y	41 (19-73)	42 (18-78)	42 (19-75)	42 (18-69)
Race, white, %	94	96	96	94
Migraine diagnosis, %				
With/without aura	24	28	27	23
With aura	9	12	8	7
Without aura	67	60	65	70
History of migraine				
Time since diagnosis, mean (range), y	17.0 (0.1-61)	16.5 (0.1-71)	16.9 (0.1-66)	16.2 (0.1-54)
Migraine attacks in previous 3 months, mean, No.	8.9	9.6	9.3	8.8
Previous sumatriptan use, %	63	65	65	61
Headache severity at baseline, %				
Moderate	75	74	71	73
Severe	25	25	27	26

The first attack treated was usually of moderate intensity, although about a quarter of patients rated their headache as severe. Most patients had grade 2 or 3 functional impairment. At least 80% reported photophobia and 64% phonophobia at baseline. About two thirds experienced nausea, but vomiting was relatively infrequent.

Headache Relief.—Headache response rates at 0.5, 1, 2, and 4 hours after the first attack are shown in Figure 2. A significantly higher proportion of patients treated with eletriptan reported a headache response at 2 hours compared to the placebo group (47%, 62%, and 59% for the 20-mg, 40-mg, and 80-mg doses, respectively, compared with 22% in the placebo group, $P < .0001$ for all eletriptan doses). Still greater responses versus placebo were obtained at 4 hours postdose: 64%, 76%, and 79% of patients had a headache response at 4 hours with 20 mg, 40 mg, and 80 mg, respectively, versus 25% with placebo ($P < .0001$).

The onset of headache response after eletriptan treatment was rapid. At 30 minutes after treatment, 9% of those taking 40-mg or 80-mg doses reported a response, compared with 4% of patients in the placebo group ($P < .05$) and 5% of those taking 20-mg eletriptan (not significant with respect to placebo). After 1 hour, headache responses were reported by 24%, 34%, and 32% of patients in the 20-mg, 40-mg, and 80-mg eletriptan groups, respectively, compared with 15% in the placebo group (20 mg, $P < .01$; 40 and 80 mg, $P < .0001$) (Figure 2).

Pain-Free Response.—Significantly more patients on eletriptan achieved a pain-free response 2 hours after treatment when compared to placebo (14%, 27%, and 27% in the 20-mg, 40-mg, and 80-mg groups, respectively, compared to 4% of those in the placebo group; $P < .001$) (Figure 3). The percentage of patients with a pain-free response was higher at 4 hours after treatment (32%, 43%, and 49% in the 20-mg, 40-mg, and 80-mg groups, respectively, compared to 12% in the placebo group, $P < .0001$) (Figure 3). There was also a rapid onset of pain-free response: 10% of patients taking 80-mg eletriptan, 7% of those taking 40 mg, and 4% of those taking 20 mg were pain-free at 1 hour after treatment. This compares with 1% of patients in the placebo group (eletriptan 20 mg and 40 mg, $P < .05$; eletriptan 80 mg, $P < .0001$) (Figure 3).

Sustained Response.—The percentages of patients who experienced headache recurrence within 24 hours of treatment for the first attack (after initial headache response within the first 2 hours) were significantly lower with eletriptan than with placebo. Recurrence rates were 31%, 29%, and 21%, respec-

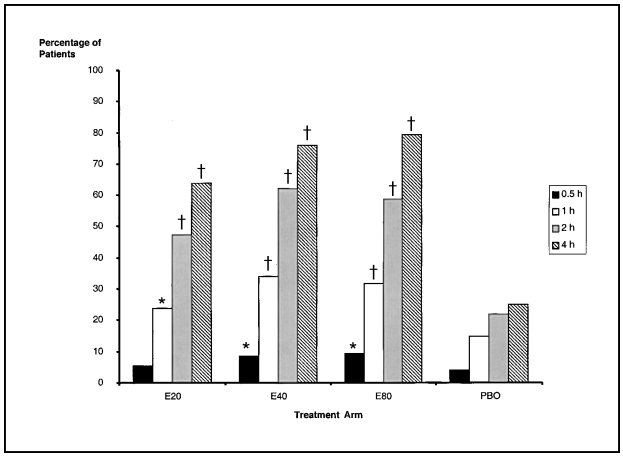

Fig 2.—Headache response rates of patients treated with eletriptan 20 mg (E20), 40 mg (E40), 80 mg (E80), or placebo (PBO) at 0.5, 1, 2, and 4 hours postdose. *$P < .05$ versus placebo at corresponding time point. †$P < .0001$ versus placebo at corresponding time point.

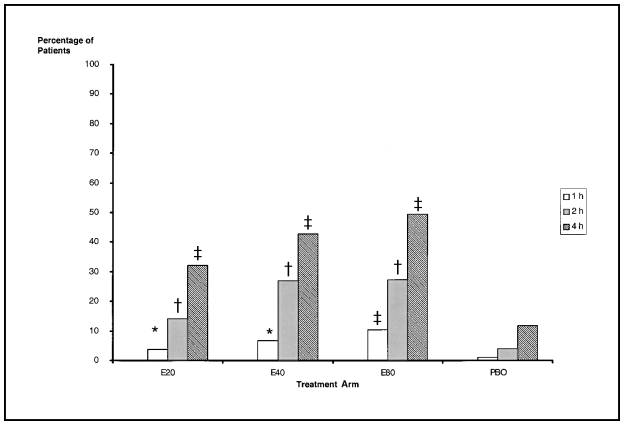

Fig 3.—Pain-free response rates of patients treated with eletriptan 20 mg (E20), 40 mg (E40), 80 mg (E80), or placebo (PBO) at 1, 2, and 4 hours postdose. *$P < .05$ versus placebo at corresponding time point. †$P < .001$ versus placebo at corresponding time point. ‡$P \leq .0001$ versus placebo at corresponding time point.

tively, for the group receiving 20 mg, 40 mg, and 80 mg of eletriptan and 36% for the group receiving placebo. Patients taking any dose of eletriptan took less rescue medication than those taking placebo (29%, 26%, and 21% in the 20-mg, 40-mg, and 80-mg groups, respectively, compared to 57% in the placebo group; $P < .001$).

To further analyze this data, post hoc analyses of sustained response and sustained pain-free response were conducted. The sustained response analysis (defined as a headache response within 2 hours with no recurrence and no use of rescue medication or a second dose of treatment medication) indicated that patients treated with eletriptan had a significantly improved response compared to those patients taking placebo (Figure 4). Patients taking eletriptan 20 mg, 40 mg, and 80 mg achieved highly significant increases over placebo (29%, 39%, 42% versus 10%, respectively; $P < .0001$). All doses of eletriptan studied also achieved significantly higher rates of sustained pain-free response (pain-free response in 2 hours with no recurrence and no use of rescue medication or second dose of treatment medication) (10%, 20%, 18% versus 3%, respectively; $P < .001$).

Consistency.—The consistency of the intrapatient headache responses induced by eletriptan across three consecutive migraine attacks is shown in Figure 5. With the 20-mg dose, 86% of patients had a response in at least one attack, 68% in at least two attacks, and 32% in all three attacks. With the 40-mg dose, 92% had a response in at least one attack, 77% in at least two attacks, and 47% responded in all three attacks. With the 80-mg dose, 91% responded in at least one attack, 82% had a response in at least two attacks, 60% of patients responded in all three attacks. Placebo response rates were 44% responding to at least one attack, 16% responding to two or more, and 8% responding to three attacks.

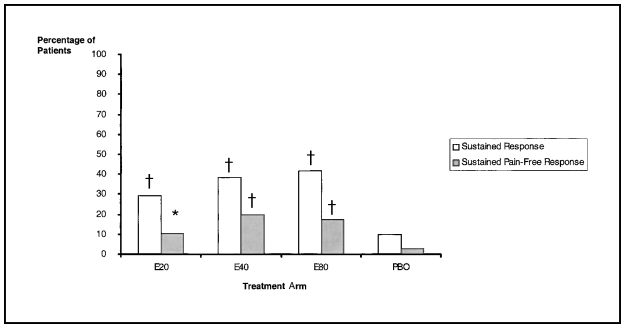

Fig 4.—Sustained response and sustained pain-free response rates of patients treated with eletriptan 20 mg (E20), 40 mg (E40), 80 mg (E80), or placebo (PBO). Sustained response was defined as response at 2 hours postdose with no recurrence, no use of a second dose of treatment medication, and no use of any rescue medication. *$P < .001$ versus placebo. †$P < .0001$ versus placebo.

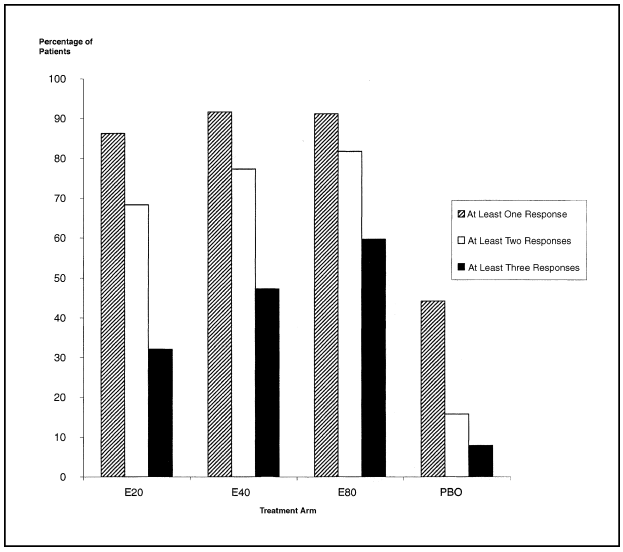

Fig 5.—Consistency of 2-hour headache response in patients treated with eletriptan 20 mg (E20), 40 mg (E40), 80 mg (E80), or placebo (PBO).

Functional Response.—All doses of eletriptan were associated with a statistically significant functional response versus placebo at 2 hours ($P < .001$) (Figure 6). Fifty-one percent, 60%, and 57% of patients taking eletriptan 20 mg, 40 mg, and 80 mg, respectively, reported a functional response 2 hours after treatment compared to 26% of those receiving placebo. The response was rapid: 27%, 32%, and 29% of patients in the three eletriptan groups had a functional response within 1 hour, compared to 19% of the placebo group (20 mg, $P < .05$; 40 and 80 mg, $P < .005$). Continued improvement in functional response versus placebo was apparent at 4 hours postdose.

Migraine-Associated Symptoms.—Table 2 summarizes the efficacy of eletriptan in relieving associated symptoms of nausea, photophobia, and phono-

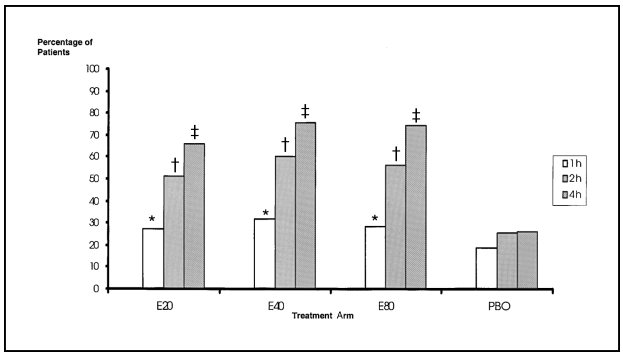

Fig 6.—Functional response rates of patients treated with eletriptan 20 mg (E20), 40 mg (E40), 80 mg (E80), or placebo (PBO) at 1, 2, and 4 hours postdose. *$P < .05$ versus placebo at corresponding time point. †$P < .001$ versus placebo at corresponding time point. ‡$P < .0001$ versus placebo at corresponding time point.

phobia. As can be seen, all three doses of eletriptan produced significantly greater relief compared to placebo in two of three associated symptoms at 1 hour, and in all three associated symptoms at 2 hours. At the 2-hour time point, 41%, 53%, and 44% of patients on the 20-mg, 40-mg, and 80-mg doses of eletriptan had achieved remission of baseline nausea, compared to 24% of patients on placebo ($P < .001$).

Adverse Events and Tolerability.—Adverse events following the first dose of study medication for attack 1 are presented here. All causality adverse events that occurred in 3% or more of patients in any group are shown in Table 3. The most common treatment-emergent adverse event was somnolence, experienced by 2.8%, 7.1%, and 8.7% of patients in the 20-mg, 40-mg, and 80-mg eletriptan groups and by 4.5% of patients in the placebo group. Overall, most adverse events were described as mild or moderate and transient in nature. The profile of adverse events after the second and third attacks was similar to that after the first attack, and the 20-mg adverse event profile was similar to placebo. Over the course of the study, 272 patients withdrew from the trial at some point after treating the first migraine attack. Most of these withdrawals (n = 222) were considered unrelated to study medication and were usually due to the patient treating fewer than 3 migraine headaches during the 3-month study period. Of the remainder, 23 patients withdrew because of insufficient clinical response and 25 withdrew due to adverse events or laboratory abnormalities judged related to study medication: 3 each from the 20-mg and 40-mg groups, 14 from the 80-mg group, and 5 from the placebo group.

Table 2.—Percent of Patients Showing Relief of Associated Symptoms on Eletriptan 20 mg, 40 mg, 80 mg, or Placebo at 1, 2, and 4 Hours Postdose

Symptom	Eletriptan 20 mg	Eletriptan 40 mg	Eletriptan 80 mg	Placebo
Nausea	(n = 177-188)	(n = 178-189)	(n = 186-195)	(n = 182-193)
1 hour	23*	31*	22	15
2 hours	41*	53†	44*	28
4 hours	58‡	70‡	67‡	34
Photophobia	(n = 218-229)	(n = 221-231)	(n = 227-243)	(n = 214-229)
1 hour	17*	21*	25‡	10
2 hours	36‡	48‡	49‡	16
4 hours	56‡	65‡	68‡	24
Phonophobia	(n = 177-190)	(n = 174-184)	(n = 184-199)	(n = 173-184)
1 hour	18	23*	26*	14
2 hours	43‡	48‡	54‡	18
4 hours	59‡	64‡	71‡	25

*$P < .05$ versus placebo at corresponding time point.
†$P < .001$ versus placebo at corresponding time point.
‡$P < .0001$ versus placebo at corresponding time point.
(Sample sizes vary depending on number of patients with assessment available at each time point.)

Table 3.—Adverse Events Occurring in 3% or More of Any Treatment Group (First Attack, All Causalities)*

Adverse Event	Eletriptan 20 mg (n = 290)	Eletriptan 40 mg (n = 296)	Eletriptan 80 mg (n = 312)	Placebo (n = 292)
Asthenia	3.1	3.4	7.1	2.7
Dizziness	2.8	5.1	6.1	3.1
Dry mouth	2.1	3.0	3.8	0.7
Dysphagia	0.3	2.4	3.2	0.3
Headache	1.0	2.4	4.8	1.7
Nausea	3.8	5.7	5.4	5.1
Somnolence	2.8	7.1	8.7	4.5
Vasodilation	0.0	2.4	3.2	1.4

*Values are percentage. Frequency shown is all treatment-emergent events in the first 4 hours after the first dose used to treat the first attack; all events with incidence of 3% or greater in any treatment group are shown.

The most common of these adverse events were asthenia (n = 3), hypertonia (n = 4), rash (n = 3), dizziness (n = 5), and chest symptoms (n = 5). None of the chest symptoms were serious or associated with ECG changes or any other clinical evidence of ischemia. There were only 8 treatment-related withdrawals after the first attack: 3 from the 20-mg group, 1 from the 40-mg group, and 4 from the placebo group. Two patients withdrew because of laboratory abnormalities (increased aspartate aminotransferase/alanine aminotransferase) that were judged to be treatment related; 1 each in the placebo and eletriptan 80-mg groups. Both abnormalities resolved within 30 days of discontinuation. There were no ECG changes that were considered to be of clinical concern and related to study treatment. There were no serious adverse events among the patients in the study that were considered related to study treatment.

Treatment Acceptability.—The subjective acceptability of the treatment was assessed by asking patients the question, "Given the choice between this and any other medication to treat a migraine attack, would you take this again?" After the first attack, 69% of patients in the 20-mg group, 74% in the 40-mg group, 68% in the 80-mg group, and 33% in the placebo group ($P <$ .001 for all comparisons) rated the study medication as an acceptable treatment for acute migraine attacks.

COMMENTS

The results of this study demonstrate that a single dose of oral eletriptan 20 mg, 40 mg, or 80 mg is a highly effective, fast-acting, and well-tolerated acute treatment for migraine. All doses of eletriptan were statistically and clinically superior to placebo for the primary 2-hour headache response and also for other efficacy endpoints relevant to migraine therapy. These included headache response at other time points, pain-free response, reduction in functional impairment, and relief from migraine-associated symptoms such as nausea, photophobia, and phonophobia. Furthermore, the onset of symptom relief was rapid, with a headache response being observed as early as 30 minutes after 40-mg and 80-mg doses of eletriptan. The 4-hour headache response rates observed here were greater than the 2-hour headache response rates for all doses of eletriptan, and were as high as 79% for the 80-mg dose compared to 25% for placebo.

An unexpected observation was that there was no notable difference in the headache response and pain-free response rates between the 40-mg and 80-mg doses. This observation is in contrast to most previous reports where an increase in efficacy has occurred in an apparent dose-related manner.[7,8,15] The reasons for the lack of a clear dose-response effect in the current study are uncertain, but may be related to the lower rate of patients reporting severe head pain at baseline, 25% to 28% in the current study compared to 45% to 50% in other trials that have shown significant dose-response effects.[7] Confirmation of this comes from a post hoc exploratory analysis that found no difference in 2-hour response for moderate versus severe headaches on the 80-mg dose of eletriptan (<2 points, based on therapeutic gain), but greater reductions in headache response (in the range of 8 to 12 points) for the 2 lower doses.

However, the 80-mg dose did demonstrate superiority over the 20-mg and 40-mg doses in domains of recurrence and intrapatient consistency.

In the present study, eletriptan was consistently effective in treating three consecutive migraine attacks. The intraindividual consistency increased with respect to dose and is remarkably similar to levels previously observed for rizatriptan. In a meta-analysis of

triptan studies, rizatriptan was shown to have superior consistency of response to the other triptans.[1] The rizatriptan data presented arises from a single article and,[16] although the study design is different from the one in this study, it is unlikely that this would make a significant alteration in the consistencies observed, thereby allowing a comparison to be made. Consistency for 80-mg eletriptan versus rizatriptan through one, two, or all three attacks was 91% versus 96%, 82% versus 86%, and 60% versus 60%, respectively. It should be noted that the consistency achieved by eletriptan in this study is higher than that presented in the triptan meta-analysis. Therefore, it is suggested that eletriptan acts in a highly consistent manner over multiple attacks, appears superior to several other triptans, and may be comparable in consistency to rizatriptan.

While headache pain is the immediate target of antimigraine therapy, many sufferers rate other effects, particularly the inability to carry out normal activities, as being more distressing than the headache itself.[17] In this trial, 51% to 60% of eletriptan-treated patients who exhibited functional impairment at baseline had a 2-grade improvement in functional impairment by 2 hours postdose, and nearly one third were able to function normally. In addition, all doses of eletriptan tested were effective in providing relief from migraine-associated symptoms such as photophobia, phonophobia, and nausea.

In the current study, rates of migraine headache recurrence after eletriptan treatment were relatively low: 31% of patients in the 20-mg group and 26% of the 40-mg group experienced headache recurrence after the first attack, and the 80-mg dose was particularly effective with only 21% of patients experiencing recurrence within 24 hours. In fact, the 21% recurrence rate with the 80-mg dose of eletriptan is lower than the published recurrence rates for sumatriptan, zolmitriptan, rizatriptan, and almotriptan.[18-23]

The exact mechanism responsible for headache recurrence is yet to be determined, but it has been suggested that it may be related to the characteristics of the drug in question, or to the underlying pathophysiology of migraine.[24] In particular, there is debate about whether the half-life of a triptan can influence the rate of recurrence. In support of this, eletriptan has been shown to have significantly faster association and slower dissociation rates than sumatriptan to the 5-HT_{1D} receptor.[25] It is also noteworthy that eletriptan does have a longer elimination half-life (4 hours) than most other currently available 5-$HT_{1B/1D}$ agonists. Naratriptan is an exception, with a half-life of 6 hours,[26] which has been suggested to account for the low rate of headache recurrence with naratriptan in a recurrence-prone population.[27]

Nonresponse to migraine therapy or recurrence after an initial response to therapy may lead patients to take rescue medications. In the present study, the percentages of patients taking rescue medications after taking a second dose of study medication (29%, 26%, and 21% at the 20-mg, 40-mg, and 80-mg doses, respectively) were significantly ($P < .001$) lower than in the placebo group (48%). The findings of this study are consistent with those obtained in previous trials of eletriptan and other 5-$HT_{1B/1D}$ agonists.

To allow for variable placebo response, the difference between drug and placebo response, ie, the "therapeutic gain," is often used for comparisons between clinical trials.[28] Previously reported randomized trials of eletriptan have shown 2-hour therapeutic gains of 33% to 43% with the 40-mg dose and 36% to 47% with the 80-mg dose,[8-10] compared to 40% with 40 mg and 37% with 80 mg in the current study. In another earlier, comparative trial, Goadsby et al found that 20-mg, 40-mg, and 80-mg oral doses of eletriptan had therapeutic gains of 31%, 41%, and 53%, respectively, at 2 hours after treatment compared to 32% for a 100-mg oral dose of sumatriptan.[7]

The oral eletriptan doses tested here showed a rapid onset of action, with a therapeutic gain at 30 minutes of 5% each in the 40-mg and 80-mg groups; and at 1 hour, 9%, 19%, and 17% with the 20-mg, 40-mg, and 80-mg doses, respectively. While eletriptan was generally well tolerated, a higher discontinuation rate was observed for the 80-mg dose during the first attack. This may reflect a limitation of the protocol: that physicians were unable to titrate patients to an acceptable dose, and that not all patients may tolerate the higher dose. There is a preliminary report from long-term studies that patients who do not respond well to eletriptan 40 mg can be successfully managed at the 80-mg dose.[29] No patients in the

80-mg treatment group who experienced the second and third migraine attacks were discontinued from the trial due to study treatment. This further supports the suggestion that those who were withdrawn after the first attack did so due to lower drug tolerability.

All doses of eletriptan met with a high level of acceptability: over 68% of patients in this study on each of the three doses said that they would take their dose again for a migraine attack. Acceptability may be viewed as a global measure of the "efficacy benefit/adverse event" ratio as perceived by the patient. All three doses of eletriptan were well tolerated. Adverse events were mostly mild to moderate and transient. It is interesting to note that the adverse event rate on placebo was consistently higher in the current study than has been reported in most other triptan trials (eg, results reported in the USPI of other triptans).[30-33] This nonspecific increase in adverse events, affecting both placebo and eletriptan, may be due to the fact that patients received a written reminder to record adverse events concurrently during the course of study treatment. This has not been reported as a standard practice in previously published triptan trials, which appear to rely on retrospective recollection at the subsequent visit with the study physician. Use of this latter recording method and associated forgetting of transient adverse events may account for the lower incidence of adverse events reported in other triptan trials. Somnolence and asthenia were the most common adverse events, showing a dose-dependent increase of 4% to 5% from the 20-mg to the 80-mg dose. Compared to sumatriptan, central nervous system (CNS) adverse events appear to be modestly higher in triptans with higher lipophilicity and (presumably) some degree of CNS penetration. It has been speculated that the ability of triptans, such as eletriptan, to reach CNS targets may offer a secondary mechanism that augments migraine efficacy, specifically increasing remission of nausea.[34]

In conclusion, all three doses of eletriptan provided effective and broad-spectrum relief of headache pain and associated symptoms, resulting in rapid restoration of normal levels of functioning. There was evidence of dose dependence on some, but not all, treatment endpoints. The 40-mg dose of eletriptan produced a very good headache response, with rapid onset and good consistency. The 80-mg dose did not increase headache or pain-free response in the current study (unlike previous reports[7,8,15]), but it was associated with increased consistency of response, as well as a reduced risk of headache recurrence. Finally, the 20-mg dose of eletriptan was an effective treatment option associated with a very low incidence of adverse events compared to placebo.

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