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Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan

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This current randomized, open-label, crossover study evaluated preference for oral eletriptan 80 mg compared with subcutaneous sumatriptan 6 mg (suma-sc) amongst patients ($n = 311$) meeting IHS criteria for migraine who had recently used suma-sc, and found it well tolerated. Three attacks were treated on each study medication. Assessment of subjective preference was evaluated, after which patients freely chose which study medication they wished to use to treat each of three additional migraine attacks. A slight majority (50.6%) preferred or greatly preferred eletriptan, whilst 43% preferred suma-sc. When permitted to choose between eletriptan and suma-sc for subsequent treatment, 78% of patients who had preferred eletriptan took eletriptan during the extension phase for all three of their attacks, whilst only 37% of patients who preferred suma-sc took suma-sc for all of their extension-phase attacks ($P < 0.05$). Secondary efficacy measures showed comparable efficacy for each study medication, except for faster headache response and pain-free rates favor of suma-sc, and a significantly lower recurrence rate on eletriptan (25% vs. 40%; $P < 0.05$). The results of this study suggest that eletriptan is a strong alternative option for patients who have been prescribed suma-sc.

Both the 40-mg (Goadsby *et al*., 2000; Mathew *et al*., 2003) and the 80-mg (Goadsby *et al*., 2000; Sandrini *et al*., 2002) doses of oral eletriptan have demonstrated superior efficacy versus oral sumatriptan 100 mg, based on the results of two placebo-controlled, head-to-head comparator studies. The efficacy advantage of eletriptan extends beyond headache response at 2 h, and includes headache response at 1 h, pain-free at 2 h, relief of associated symptoms at 2 h, return to functioning at 2 h and sustained response at 24 h. Consistent with the multidimensional advantage of eletriptan, patients expressed a higher preference for eletriptan compared with oral sumatriptan, again, in two or more studies (Goadsby *et al*., 2000; Sandrini *et al*., 2002; Mathew *et al*., 2003).

Since its introduction in 1991, the 6-mg dose of sumatriptan administered subcutaneously has been the benchmark for all acute migraine treatments in terms of speed of onset and degree of relief (Perry and Markham, 1998; Oldman *et al*., 2002). A meta-analysis of placebo-controlled trials found subcutaneous sumatriptan (suma-sc) to rank first amongst all triptans in terms of speed of onset, with a 1-h headache response rate of 70% (vs. 22% on placebo), and in terms of remission, with a 2-h pain-free rate of 60% (vs. 12% on placebo) (Oldman *et al*., 2002). In fact, individual studies (Cady *et al*., 1991) have shown significant efficacy versus placebo as early as 10 min.

Reports of what migraine patients are looking for in an acute treatment cite speed of onset (typically < 1 h) and complete relief as the two most sought-after characteristics of the ideal migraine medicine (Silberstein, 1995; MacGregor, 1997; Davies *et al*., 1998; Dahlöf, 2001; Lipton *et al*., 2002).

Whilst patient preference lacks clear operationalized criteria and thus may be considered the least scientific of all endpoints, there is a growing recognition that clinical trials research neglects this dimension at its peril (Davis *et al*., 2002; Dodick, 2002). Patient preference appears to be highly correlated with compliance, and without good compliance, any acute treatment for migraine, regardless of its proven efficacy in clinical trials, cannot be an effective treatment.

Suma-sc has never, to our knowledge, been directly compared with an oral triptan in terms of treatment satisfaction or patient preference. In a previous open-label crossover study, suma-sc was rated by patients as being significantly superior to 'usual care' in meeting efficacy expectations (Bouchard *et al*., 1997).

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Eighty-nine percent of patients indicated that they 'would use sumatriptan again in the future,' but noted that 'usual care' treatments were 'easier' to use by a 20% margin.

The goal of the current study was to evaluate patient preference for the 80-mg dose of oral eletriptan compared to suma-sc. To ensure that the comparison afforded a fair test of eletriptan preference, patients were only permitted to enter the study if they had taken suma-sc in the previous year and found it to be an acceptable treatment. An additional goal of the study was to compare how subjective preference correlated with the elective choice of which study medication to continue treatment within a three-attack extension phase.

Patients and methods

Patients

Male and female patients were permitted to enter the study if they were 18–65 years of age (inclusive), met the International Headache Society criteria for migraine with or without aura (Headache Classification Committee of the International Headache Society, 1988), and suffered at least one acute attack every 6 weeks. Patients were also required to have been treated with suma-sc at some time in the previous year. Patients were excluded for the following reasons: poor tolerance to suma-sc; presence of frequent concurrent non-migrainous headache and/or treatment-resistant migraine or migraine variants (e.g. familial hemiplegic or basilar migraine); known history of coronary artery disease, clinically significant arrhythmia, heart failure or uncontrolled hypertension; any clinically significant medical illness or laboratory abnormalities; severe reduction in gastrointestinal absorption; hypersensitivity or known contraindication to treatment with eletriptan or sumatriptan; concomitant use (in the 4 weeks prior to study treatment) of a potent CYP3A4 inhibitor or use (in the 48 h prior to study treatment) of monoamine oxidase (MAO) inhibitors; misuse or abuse of alcohol or other substances, including analgesics or ergotamine; use of any experimental drug within the past month; and women who were pregnant or breast-feeding.

At screening, all patients had a physical examination, including blood pressure, 12-lead ECG, and urine pregnancy testing (as appropriate). Study conduct was consistent with the Declaration of Helsinki. The study protocol was approved by appropriate Institutional Review Boards (Ethics Committees) at each site. The study was explained to prospective patients, and written informed consent was obtained prior to study entry.

Study design

This randomized, open-label, crossover study was conducted at 34 centers in nine countries. Patients were randomly assigned to one of two treatment sequences:

Treatment sequence	Treatment period 1	Treatment period 2
A	Suma-sc 6 mg for three attacks	Oral eletriptan 80 mg for three attacks
B	Oral eletriptan 80 mg for three attacks	Suma-sc 6 mg for three attacks

Each treatment period lasted for a maximum of 16 weeks or until three migraine attacks had been treated with study medication, whichever occurred sooner. The crossover phase of the study was followed by an optional extension phase in which patients were dispensed both eletriptan and sumatriptan, and thus were given the opportunity to choose which study medication they wished to use to treat each of the three additional migraine attacks.

Patients took study medication within 6 h of the onset of migraine headache pain, as long as the aura phase had ended and the pain was moderate or severe in intensity and not improving. Study medication was not to be taken if the patient had already self-medicated in the previous 6 h with an analgesic or antiemetic; or in the previous 48 h with another triptan, or an ergotamine-containing or ergot-type medication.

Patients recorded migraine-related symptoms in a diary at baseline (immediately pre-dose), and at 30 min, 1 h, 1.5 h, 2 h, 4 h and 24 h after dosing. Use of rescue medications was also recorded in the diary.

Patients who failed to achieve a headache response by 4 h were permitted to take rescue medication, but were not permitted to take any other triptan, ergotamine or ergotamine-like substance for 24 h post-dose. Patients who achieved a 2-h headache response but experienced a recurrence were permitted to take a second dose of study medication, provided at least 4 h had elapsed since the first dose was taken. The time of recurrence and the second dose, and information on rescue medication, were noted in the diary card. Headache intensity was recorded immediately prior to taking the second dose of study medication. Rescue medication was permitted 4 h after this second dosing if needed. Within 48 h of study treatment, the patient was asked to contact the investigator or his representative to review adverse event information, and to schedule the final appointment, which took place within 14 days of the final attack.

Evaluation of efficacy

The primary outcome measure of the study was patient preference for eletriptan versus suma-sc. Preference was evaluated during the follow-up visit at the end of the crossover phase, and again at the end of the optional extension phase. Preference was assessed using the following two questions: (i) 'based on your total experience with the two medications used during this study, which do you prefer overall?' The response was rated on a 5-point scale: 'greatly preferred' or 'somewhat preferred' either study drug, or 'no preference' for either study drug and (ii) 'what was the main reason for your preference?' The response choices consisted of: (a) speed of onset; (b) lack of recurrence; (c) degree of relief; (d) ease of use; (e) absence of side-effects; (f) type of medication (injected versus oral); or (g) other.

Secondary outcomes consisted of the following: (i) change from pretreatment baseline in headache intensity (headache intensity was rated on a 4-point global scale: none, mild, moderate, severe); (ii) change from pretreatment baseline in a 5-point patient-rated Global Impression of Efficacy scale (ranging from 'much worse' to 'much improved'); (iii) the presence or absence of the associated symptoms: nausea, vomiting, photophobia and phonophobia; (iv) change from pretreatment baseline in a 4-point functional impairment scale (3 = bed rest; 2 = severe impairment in work, study or housekeeping activities, but not requiring bed rest; 1 = some impairment in work, study or housekeeping activities; 0 = normal level of functioning (even if headache is present) – change was reported as the percent of patients whose functional status improved from 2–3 to 0–1 in their functioning; (v) headache recurrence (and time to headache recurrence), defined as the return of a moderate to severe headache (from a previously improved level of mild or no headache) between 2 and 24 h after ingestion of study medication; (vi) time to use of rescue medication; (vii) sustained relief, defined as headache response within 2 h after study treatment, with no subsequent headache recurrence or use of rescue medication within 24 h after the first dose of study medication; and (viii) acceptability of study medication, which was defined by the patient's answer to the following question: 'given the choice between this and any other previous medication you have used to treat a migraine attack, would you take this again?'

The percent of patients who were headache responders was defined as any patient who, 2 h post-treatment, reported improvement in headache intensity to mild or pain-free levels from a pretreatment level of moderate or severe.

Statistical analyses

The primary endpoint of this study was patient preference for eletriptan versus suma-sc at the end of the crossover phase. Patients who answered 'greatly preferred eletriptan' or 'somewhat preferred eletriptan' (scores 1 or 2) were categorized as preferring eletriptan. Similarly, patients who 'greatly preferred sumatriptan' or 'somewhat preferred sumatriptan' (scores 4 or 5) were categorized as preferring suma-sc. Patients who had 'no preference' (score of 3) were categorized separately as 'no preference.' The number of patients in each sequence group who preferred either the treatment they received in the first period or the treatment they received in the second period were summarized in a 2×2 table, and the Mainland-Gart test was used to compare the two treatment groups, by considering the preferred treatment for period 1 and 2. The binary variable response to treatment (with values of responder or non-responder) at 2 h post-dose were analyzed for each attack using a categorical linear model. The data from the first attack in each period of the crossover phase were pooled together, as were data from the second and third attacks. The model included effects for patient, treatment and period. The baseline severity of headache at each attack was also included as a covariate.

Results

Patient sample

A total of 323 patients were screened (Fig. 1), of whom 148 were randomized to treat the first three attacks (period 1) with eletriptan, and 163 were randomized to treat the first three attacks with suma-sc. Patients treated with eletriptan were then crossed over ($n = 137$) to treat the next three attacks with suma-sc (period 2), whilst patients treated with suma-sc during period 1 were crossed over ($n = 155$) to treat the next three attacks with eletriptan. There was no significant difference in the demographic or clinical characteristics of study patients assigned to either treatment sequence, period 1 (eletriptan → suma-sc), or period 2 (suma-sc → eletriptan) (Table 1).

At the end of period 2, 218 patients (70.1%) of those initially randomized elected to enter the extension phase (Fig. 1), in which up to three additional attacks could be treated. The clinical features of study completers who elected to enter the extension phase were similar to the original study sample: 85% female; mean age, 42.1 ± 10.2 years; 71% without aura; 89% of recent pre-study attacks rated as moderate to severe in intensity.

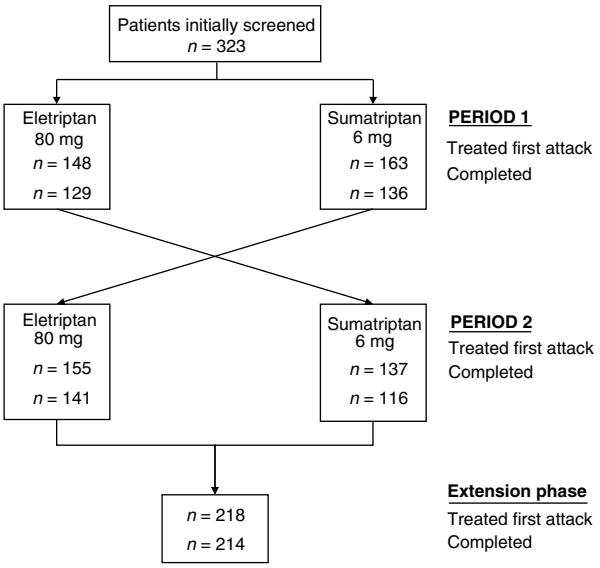

Figure 1 Patient disposition.

Patient preference: eletriptan versus subcutaneous sumatriptan

Patient preference was assessed at the end of the crossover phase using two methods: subjective patient ratings, and elective choice of drug for use in the extension phase. A slight (non-significant) majority of patients (50.6%) preferred or greatly preferred eletriptan, whilst 43% preferred suma-sc (Fig. 2a). No order effect was observed in the current study.

Amongst patients who preferred eletriptan, five reasons were cited by 83% or more of patients: ease of use, absence of adverse events, route of administration, lack of recurrence, and degree of relief. Amongst patients who preferred suma-sc, two reasons were overwhelmingly cited (by 90% of the sample) for preferring suma-sc: speed of onset and degree of relief.

When permitted to choose between eletriptan and suma-sc for extension-phase treatment, 78% of patients with a stated preference for eletriptan took eletriptan during the extension phase for all three of their attacks (Fig. 2b), whilst only 37% of patients with a stated preference for suma-sc took suma-sc for all of their extension-phase attacks ($P < 0.05$). A similarly higher proportion of patients treated two of three attacks with their preferred drug: eletriptan, 95% versus suma-sc, 63%.

Nineteen patients (6.5%) reported no preference at the end of the crossover period. Twelve of these 19 patients continued into the extension phase, choosing to treat 29/35 attacks (83%) with eletriptan.

Headache response and pain-free response

Treatment with suma-sc was associated with an earlier headache response (Fig. 3a) and pain-free response (Fig. 3b) than eletriptan. Both headache response and pain-free rates were convergent by 2 h post-dose.

Relief of associated symptoms

Treatment with eletriptan and suma-sc were both associated with high levels of relief of associated symptoms, as indicated by absence of nausea (Fig. 4a), photophobia (Fig. 4b) and phonophobia (Fig. 4c). Once again, treatment with suma-sc was associated with higher absence rates in the first hour post-dose, with absence rates for both drugs converging by 2 h.

Outcome at 24 h

There was a significantly lower recurrence rate amongst patients treated with eletriptan (25%) compared with suma-sc (40%; $P < 0.05$). Overall, sustained headache

Table 1 Clinical characteristics of the patient sample

	Sequence A Eletriptan → suma-sc (n = 148)	Sequence B Suma-sc → eletriptan (n = 163)
Female	84%	80%
Age [years (mean ± SD)]	41.3 ± 10.1	42.0 ± 10.0
Range (years)	18–63	19–64
Duration of illness [years[a] (mean ± SD)]	15.4 ± 12.2	13.8 ± 11.9
Migraine subtype		
Without aura	78.4%	71.2%
With aura	8.1%	6.7%
Mixed	13.5%	22.1%
Mean (±SD) frequency of migraine attacks over previous 3 months	8.5 ± 4.3	8.9 ± 3.9
Attacks rated as moderate to severe	88%	88%

[a]Time since first diagnosis.

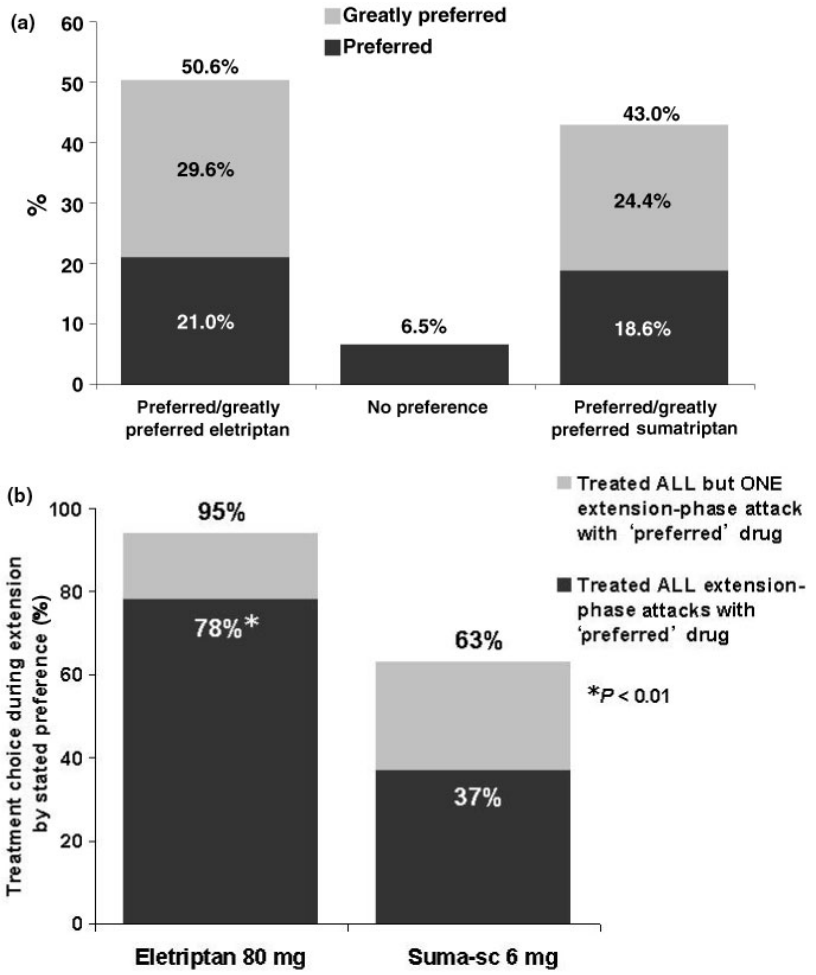

Figure 2 (a) Patient preference for eletriptan 80 mg versus suma-sc 6 mg: crossover phase results. (b) Choice[a] of drug to treat extension-phase attacks: relationship to patient preference rating at the end of the crossover phase. [a]Nineteen patients excluded who expressed no preference during the crossover phase.

response and pain-free rates at 24 h were comparable for eletriptan compared with suma-sc (Fig. 5).

Consistency of response

Amongst patients who treated three attacks each, there was very good consistency of response (Fig. 6), with headache response achieved by 2 h in three of three attacks by 66% of patients on eletriptan compared with 72% on suma-sc. Similarly, 83 and 88% of patients, respectively, achieved a 2-h headache response in two of three attacks ($P < 0.05$).

Tolerability

Both eletriptan and suma-sc were well tolerated, with most adverse events being mild and transient (Table 2). No serious treatment-related adverse events occurred with either drug. An adverse event rated by patients as severe was reported in 6.5% of attacks treated with eletriptan and in 10.1% of attacks treated with suma-sc. This difference in the average per-attack incidence of severe adverse events continued into the extension phase, with a lower rate reported on eletriptan (1.6%) compared with suma-sc (10.9%).

Treatment acceptability

The acceptability of eletriptan was evaluated at the completion of the treatment period. The majority (80%) of patients rated eletriptan as 'entirely' acceptable (43%) or 'somewhat' acceptable (37%). A minority rated eletriptan as 'somewhat' unacceptable (9%) or 'entirely' unacceptable (5%), whilst 6% were 'uncertain'.

Factors determining patient preference

Within-patient differences in treatment response were evaluated in an exploratory attempt to understand which variables contributed to patient-rated preference (at the end of the crossover phase) and drug choice (during the extension phase). Specifically, we evaluated whether patient preference or actual drug choice (for the first treated attack after the crossover phase) were

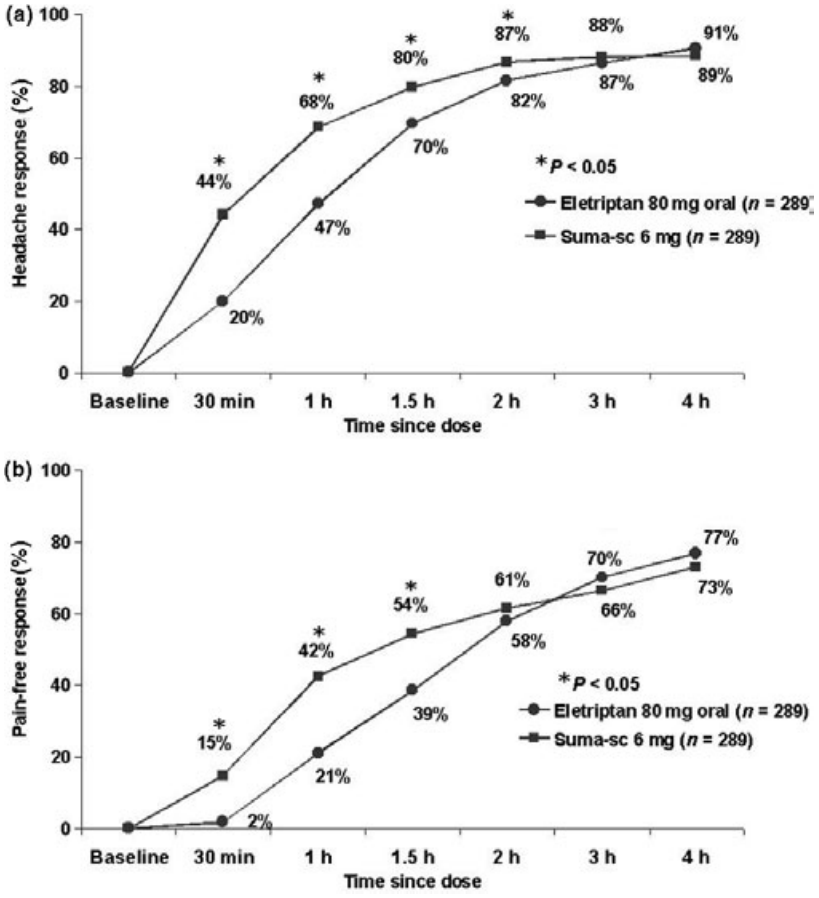

Figure 3 (a) Headache response rates in the first 4 h post-dose: eletriptan 80 mg versus suma-sc 6 mg. (b) Pain-free response rates in the first 4 h post-dose: eletriptan 80 mg versus suma-sc 6 mg.

associated with early (1 h) headache response or complete response at 2 h (defined as pain-free, and with no associated symptoms and no functional impairment). Amongst patients who achieved a complete response at 2 h in two of three attacks on both drugs during the crossover phase, eletriptan was significantly more probably to be preferred (62% vs. 38%; $P < 0.05$), and was significantly more probably to be chosen as the drug used to treat the first post-crossover attack (81% vs. 19%; $P < 0.05$; Fig. 7). Amongst patients who demonstrated headache response at 1 h in two of three attacks on suma-sc, but failed to achieve similarly early response on eletriptan, eletriptan was still preferred over suma-sc (58% vs. 42%); similarly, eletriptan was also more frequently the drug chosen to treat the first post-crossover phase attack (71% vs. 29%; Fig. 7).

Discussion

This is the first study we are aware of that has directly evaluated, using a crossover design, preference for an oral triptan compared with subcutaneously administered sumatriptan, considered to be the efficacy benchmark for all triptans. As expected, headache response and pain-free rates were faster on suma-sc compared with eletriptan. The difference represented an approximate 30-min lag time in efficacy. For example, the 44% response rate at 30 min on suma-sc was matched by a 47% response rate at 60 min on eletriptan (Fig. 3a). By 2 h, headache response rates for both treatments were convergent. Improvement slopes for associated symptoms were nearly similar from baseline onward.

On the primary outcome measure, patient preference, 51% of patients preferred eletriptan (30% greatly), whilst 43% preferred suma-sc (19% greatly). No preference was expressed by 6.5% of patients. Regardless of stated preference, patients were permitted to freely choose which study drug to take in an open extension phase in which up to three attacks were treated. Given a free choice, 37% of the subgroup of patients who preferred suma-sc nonetheless chose to take eletriptan for the majority of their attacks, and an additional 26% chose to take eletriptan for at least one of their extension-phase attacks. In contrast, 94% of patients with a stated preference for eletriptan acted on their

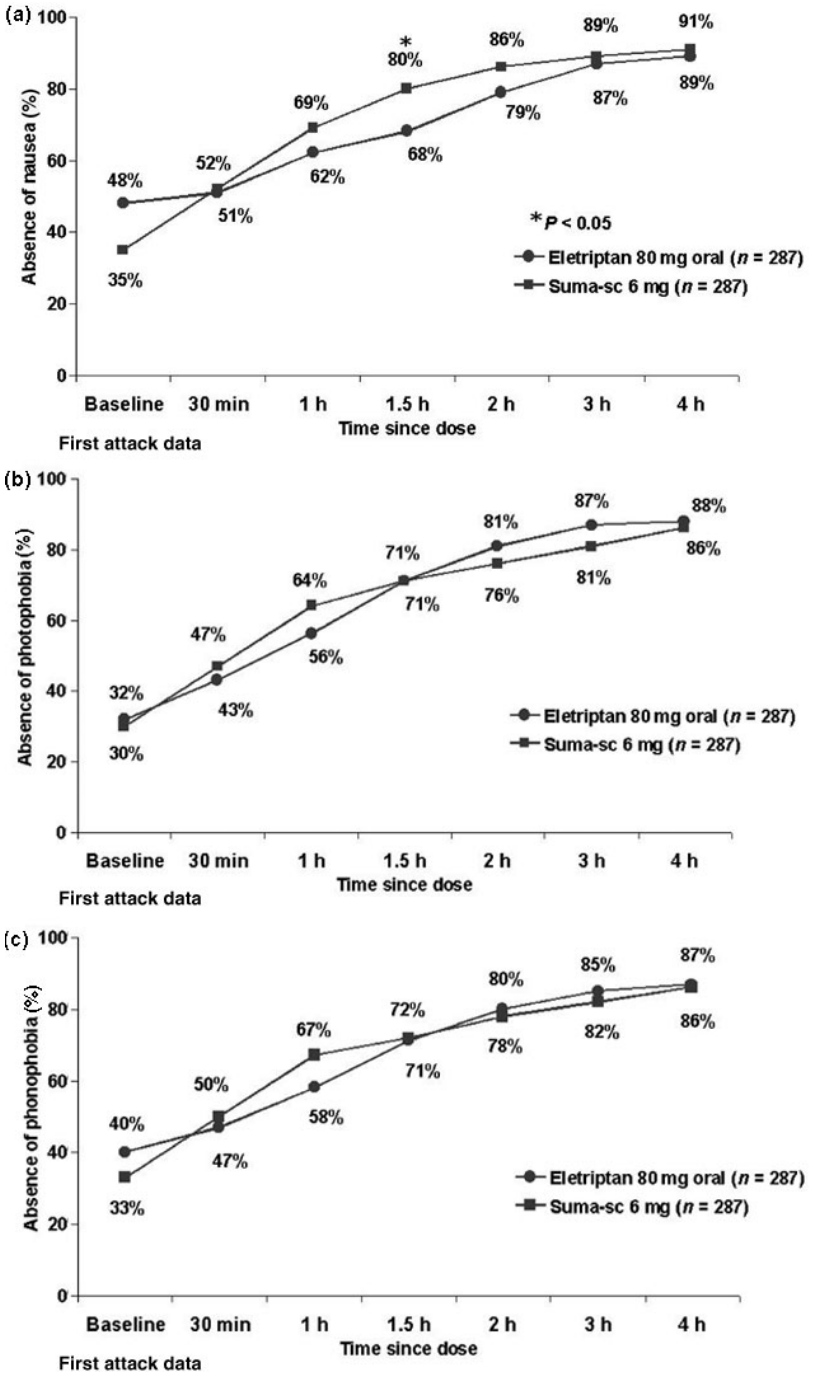

Figure 4 (a) Proportion of patients reporting absence of nausea in the first 4 h post-dose: eletriptan 80 mg versus suma-sc 6 mg. (b) Proportion of patients reporting absence of photophobia in the first 4 h post-dose: eletriptan 80 mg versus suma-sc 6 mg. (c) Proportion of patients reporting absence of phonophobia in the first 4 h post-dose: eletriptan 80 mg versus suma-sc 6 mg.

preference and treated at least two of three attacks with eletriptan.

This drug choice finding adds an important dimension to traditional subjective preference studies, and has implications for patient compliance with prescribed treatment. The current results favoring eletriptan are especially impressive since recruitment into the study was limited to patients who had recently been treated with suma-sc, thus excluding individuals who might not tolerate or elect to use a drug administered subcutaneously. Nonetheless, it is possible that a subgroup of patients might have entered the study despite dissatisfaction with prior suma-sc therapy. The earlier onset of pain relief achieved by suma-sc compared with eletriptan was not associated with higher patient preference, or higher elective choice of drug (Fig. 7). As noted previously (MacGregor, 1997; Dodick, 2002), an acute treatment for migraine, no matter how effective it may

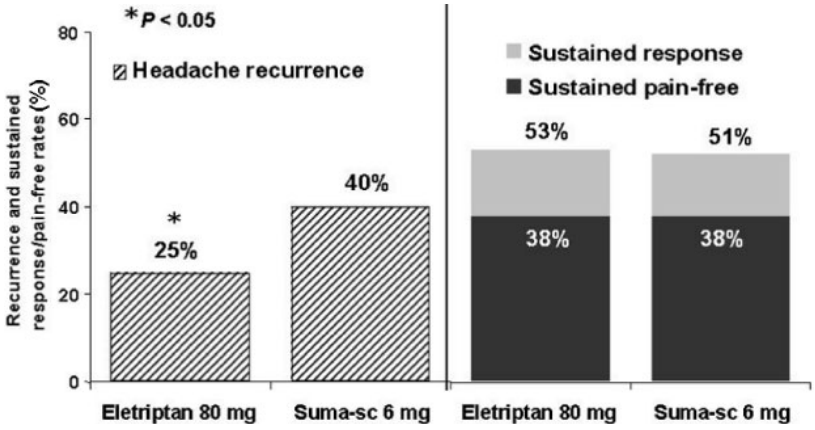

Figure 5 Headache recurrence and sustained response/pain-free: three-attack average rates for eletriptan 80 mg versus suma-sc 6 mg.

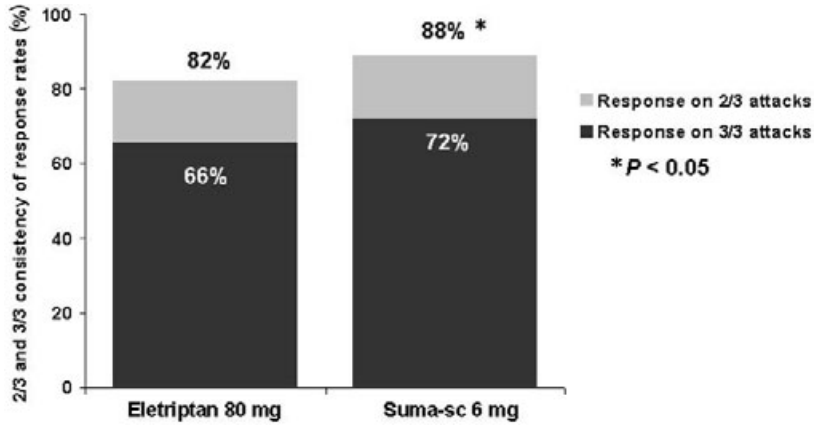

Figure 6 Consistency of headache response across three crossover phase attacks: eletriptan 80 mg versus suma-sc 6 mg/day.

Table 2 Treatment-emergent adverse events

	Eletriptan 80 mg attacks (%) $n = 863$		Subcutaneous sumatriptan 6 mg attacks (%) $n = 833$	
	Mild-Mod	Severe	Mild-Mod	Severe
Asthenia	5.3	0.8	3.7	0.1
Chest pain	1.9	0.0	5.5	0.8
Dysphagia	4.3	0.1	2.2	0.4
Nausea	10.9	1.0	5.2	0.8
Vomiting	4.2	0.2	3.7	0.4
Dizziness	2.9	0.1	2.5	0.0
Paresthesias	1.9	0.4	4.0	1.4
Patients with any severe AE (per-attack average)	6.5		10.1	

AE, adverse event.
Mild-mod, mild to moderate.

be in a research setting, has no benefit whatsoever if patients elect not to take it.

On secondary outcomes, suma-sc and eletriptan demonstrated comparable efficacy, including consistency of response (88% vs. 83%, respectively, in two of three attacks), and sustained pain-free response (38% for each drug). Headache recurrence rates were significantly lower for eletriptan (25%) compared with suma-sc (40%), a recurrence rate similar to what has been reported in other published studies of suma-sc (Perry and Markham, 1998). Finally, tolerability of eletriptan and suma-sc were comparable in terms of individual adverse events (Table 2), though as noted earlier, these results must be interpreted with caution as study entry was limited to patients who had recently used suma-sc and found it be acceptably tolerated. Despite comparable adverse event profiles, superior tolerability was one of the top reasons cited by patients who preferred eletriptan, but was not cited by patients stating a preference for sumatriptan. This might partially be attributable to the lower incidence of severe adverse events on eletriptan (6% vs. 10%). It appears, though, that preference and elective choice of drug are providing a more sensitive global measure of what patients perceive as subjectively important in terms of both tolerability and efficacy.

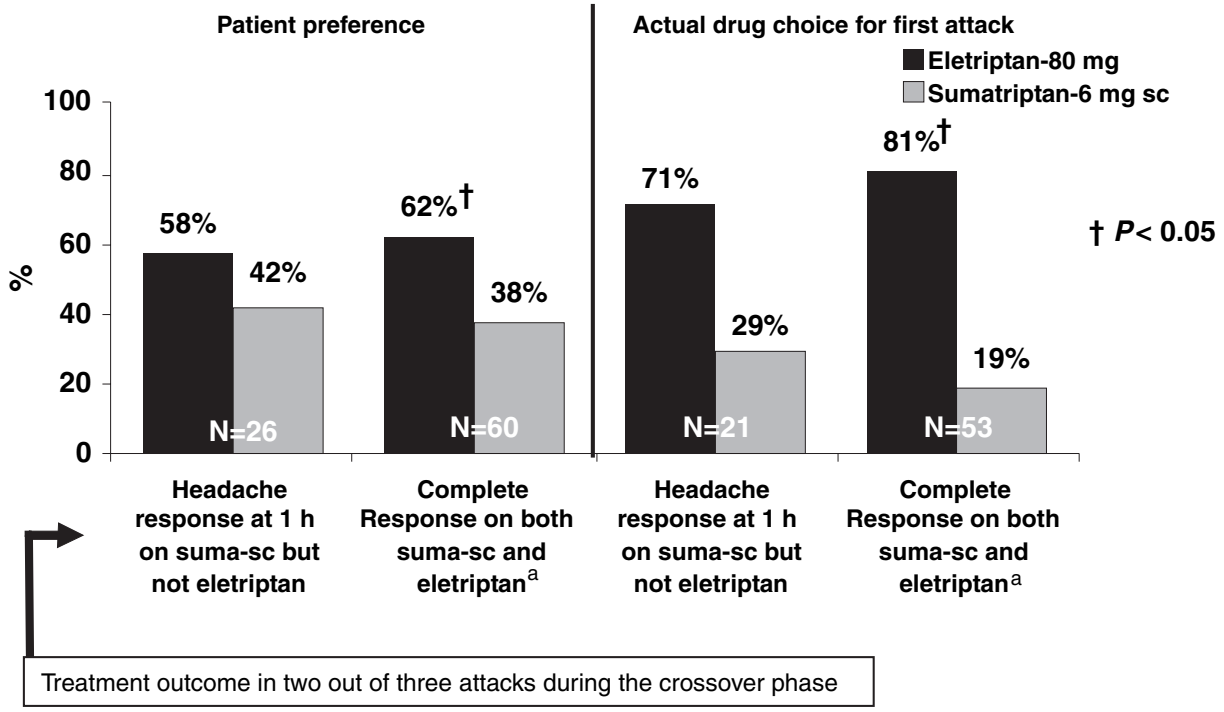

Figure 7 Influence of treatment response on patient preference and choice of triptan to treat the first open-label attack: results of a pilot analysis. [a]Complete response: pain-free response + no associated symptoms + no functional impairment at 2 h in two of three attacks on both eletriptan and sumatriptan.

The main limitation of the current study is lack of a double-blind methodology, which could have been accomplished with a double-dummy design. This limitation, however, only applies to the secondary efficacy measures. In contrast, the primary outcome measure, patient preference, could only be adequately evaluated using a randomized, open-label, crossover design in which patients could compare the global effects of drug, as well as route of administration. As Sheftell and Fox have noted, 'patient preference is an integrated, complex pattern of biological phenomenon that they experience; this pattern depends on disease state and its variability, and wanted and unwanted effects of the drug' (Sheftell and Fox, 2000).

In conclusion, patients treated with both suma-sc and eletriptan expressed a modest, but non-significantly greater, subjective preference for eletriptan. When permitted to freely choose which drug to use for the treatment of subsequent attacks, patients chose eletriptan at a significantly higher rate.

Comparable overall efficacy (except speed of onset) and significantly higher patient choice make eletriptan 80 mg a strong alternative option for patients who have been prescribed subcutaneous sumatriptan.

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