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The 40-mg dose of eletriptan: comparative efficacy and tolerability versus sumatriptan 100 mg

Hans-Christoph Diener[a], Robert Ryan[b], Wei Sun[c] and Jayasena Hettiarachchi[c]

[a]*Department of Neurology, University of Essen, Essen, Germany;* [b]*Ryan Headache Center, St Louis, MO, USA; and* [c]*Pfizer Inc., New York, NY, USA*

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Meta-analysis provides valuable information regarding relative efficacies of triptans, but head-to-head comparator studies remain the gold standard. Three similar head-to-head trials comparing eletriptan 40 mg (E40) with sumatriptan 100 mg (S100) provide a rare opportunity and sufficient power, for robust comparisons of efficacy. Data were combined from three double-blind, placebo-controlled, first-dose, first-attack acute migraine treatment studies comparing E40 ($n = 1132$), S100 ($n = 1129$), and placebo ($n = 645$). The primary outcome was headache response at 2 h. Secondary outcomes included headache response at 1 h, pain-free and functional responses, and sustained headache and pain-free responses. Odds ratios were calculated for summary estimates of probability of response. There were higher headache response rates with eletriptan versus sumatriptan at 2 h (67% vs. 57%; $P < 0.0001$) and 1 h (34% vs. 26%; $P < 0.0001$). Eletriptan also had higher 2 h pain-free (35% vs. 25%; $P < 0.0001$) and functional responses (67% vs. 58%; $P < 0.0001$). Sustained headache (42%) and pain-free (22%) response rates were higher for eletriptan versus sumatriptan (34%, $P < 0.0001$; 15%, $P < 0.0001$). The probability of response for eletriptan versus sumatriptan ranged from 36% higher (relief of nausea) to 64% higher (sustained pain-free rate). Combined analysis demonstrates that E40 has superior efficacy versus S100 across all clinically relevant outcomes.

Introduction

Migraine is a very common illness, with a prevalence of 17% in women and 6% in men (Lipton *et al*., 2002). As migraine is associated with increased seeking of medical help (Joish *et al*., 2000), the prevalence of migraine is even higher in the primary care setting, with at least one-third of all primary care patients under 50 years of age being diagnosed (Couch *et al*., 2003).

Migraines are frequent and disabling: 25% of sufferers report an average of at least one attack per week, and the average migraineur reports of having one or two per month (Lipton *et al*., 2001). During a migraine attack, 50% of individuals have severe functional impairment and/or require complete bed rest (Lipton *et al*., 2001). Overall, the impairment and impact of migraine on a patient's health-related quality of life are substantial, and are equivalent (if not greater) than those of other chronic medical illnesses such as angina, diabetes, and hypertension. As a result, the World Health Organization (WHO) ranks migraine amongst the world's top 20 most disabling medical illnesses (WHO, 2001).

The introduction of sumatriptan, the first medication in the triptan class, ushered in a new era in the targeted treatment of migraine. Since then, no triptan has been shown to consistently demonstrate significantly superior efficacy versus sumatriptan based on the results of double-blind, placebo-controlled, head-to-head comparator trials (Visser *et al*., 1996; Goldstein *et al*., 1998; Tfelt-Hansen *et al*., 1998; Gallagher *et al*., 2000; Geraud *et al*., 2000; Gobel *et al*., 2000; Havanka *et al*., 2000; Tfelt-Hansen *et al*., 2000; Lines *et al*., 2001; Dowson and Charlesworth, 2002b; Dowson *et al*., 2002a; Geraud *et al*., 2002). Although head-to-head comparator trials are considered the gold standard for assessing comparative efficacy, the relative lack of multiple large, placebo-controlled, head-to-head trials of triptans has led to the use of meta-analysis to provide comparative data. Widely publicized recent meta-analyses (Tfelt-Hansen *et al*., 2000; Ferrari *et al*., 2001; Oldman *et al*., 2002) suggest that rizatriptan and eletriptan may have superior efficacy to sumatriptan, but only at selected doses (80 mg for eletriptan and 10 mg for rizatriptan). The importance of confirming meta-analytic results based on head-to-head trials (LeLorier *et al*., 1997) is illustrated by the lack of superiority of the 10-mg dose of rizatriptan when it was *directly*

Correspondence: Hans-Christoph Diener MD, Department of Neurology, University of Essen, Hufelandstr. 55; 45122 Essen, Germany (fax: +49 201 723 5901; e-mail: h.diener@uni-essen.de).

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compared with sumatriptan in three of four head-to-head trials (Visser *et al.*, 1996; Goldstein *et al.*, 1998; Tfelt-Hansen *et al.*, 1998; Lines *et al.*, 2001). A recently available head-to-head trial comparing the 40-mg dose of eletriptan and the 100-mg dose of sumatriptan more than doubled the sample size for eletriptan 40 mg (E40) reported in the original meta-analyses (Mathew *et al.*, 2003). Therefore, the goal of the current investigation is to provide an updated analysis that specifically tests the comparative efficacy and tolerability of these two widely used doses of eletriptan and sumatriptan.

Eletriptan, a newer triptan with rapid and consistent absorption following oral administration, has high bioavailability (50%), a longer half-life than sumatriptan (4–5 h versus 2 h) and potent agonist activity at 5-$HT_{1B/1D}$ receptors (Napier *et al.*, 1999; Gupta *et al.*, 2000; Johnson *et al.*, 2001).

Three separate double-blind, placebo-controlled clinical trials (Goadsby *et al.*, 2000; Sandrini *et al.*, 2002; Mathew *et al.*, 2003) compared the efficacy and tolerability of the 40-mg dose of eletriptan to the highest recommended dose of sumatriptan 100 mg (S100) (Fig. 1), although only one (Mathew *et al.*, 2003) was specifically powered to examine this as the primary outcome measure. In two of these studies (Sandrini *et al.*, 2002; Mathew *et al.*, 2003), E40 demonstrated significant superiority for headache response, whilst the third study (Goadsby *et al.*, 2000) just missed the significance. We summarize here the results of a new analysis of combined data from these three studies. Combining data (i.e. pooling) increases the ability to detect clinically important differences on secondary outcome measures that individual studies were not powered to fully evaluate. The larger sample sizes that result from combining data also significantly increase the precision of the estimate of the true difference between two treatments on all clinically relevant outcome measures.

Methods

Patient sample

Data for the current analysis were pooled from three separate multicenter studies comparing the efficacy and tolerability of eletriptan versus S100 for the acute treatment of migraine headaches. All three studies had almost identical entry criteria, design, and outcome measures, as described in detail in the original reports (Goadsby *et al.*, 2000; Sandrini *et al.*, 2002; Mathew *et al.*, 2003). Briefly, adult patients were enrolled if they met the International Headache Society criteria for migraine (Headache Classification Committee of the International Headache Society, 1988) with or without aura, and reported a monthly frequency of one to six attacks. Key exclusion criteria consisted of coronary artery disease, heart failure, uncontrolled hypertension or abnormal electrocardiogram (ECG); hypersensitivity or known contraindication to treatment with eletriptan or sumatriptan; misuse or abuse of alcohol or other substances, including analgesics or ergotamine; and women who were pregnant or breast-feeding. The study protocols were approved by Institutional Review Boards (Ethics Committees) at each site. The study was explained to prospective patients and written informed consent was obtained prior to entering the study.

Study design

Each study used a randomized, placebo-controlled, parallel-group, double-dummy design in which the double-blind was maintained by matching plain white film-coated tablets of eletriptan to placebo tablets, and gelatin capsules containing sumatriptan to matching placebo capsules. The blinded sumatriptan was demonstrated to be both bioequivalent and clinically

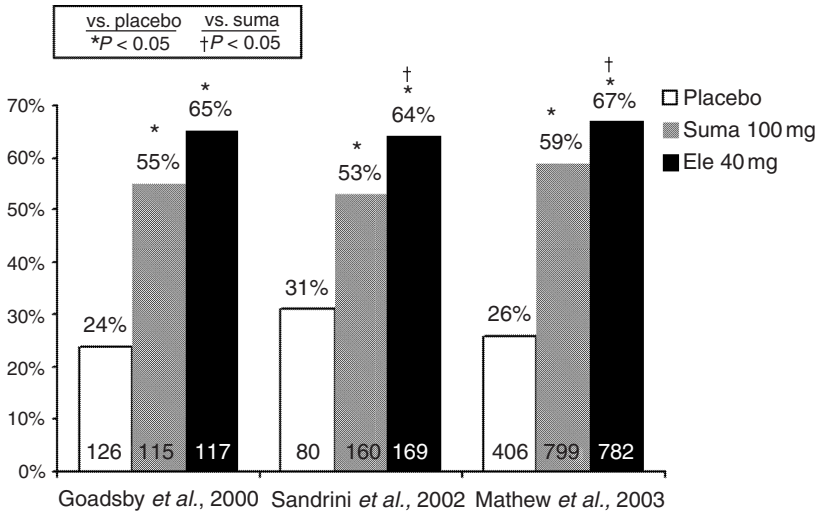

Figure 1 Headache response at 2 h in individual studies. Suma, sumatriptan; ele, eletriptan.

equivalent to the commercial tablet based on five categories of data: (i) an *in vitro* dissolution study conducted in deionized water (Milton *et al*., 2001), (ii) an *in vivo* gamma scintigraphy study showing dissolution (Wilding *et al*., 2003), (iii) bioequivalence studies meeting standard regulatory criteria for equivalent AUC and C_{max} values (Milton *et al*., 2001); (iv) a pooled analysis of three bioequivalence studies confirming early bioequivalence at the 2-h time point (AUC_{0-2h}; data on file, Pfizer Inc.); and (v) a *post hoc* comparison of the therapeutic gain for headache response at 2 h. In the current pooled analysis, encapsulated sumatriptan showed a 2-h headache response (and therapeutic gain) of 57.5% (31.2%), which is equivalent to what has been reported across all available placebo-controlled studies of the 100-mg dose of sumatriptan, 59% (29%) (Ferrari *et al*., 2001).

Evaluation of efficacy

Primary efficacy end-points consisted of the percent of patients who had a headache response, defined as improvement 2 h (Goadsby *et al*., 2000; Mathew *et al*., 2003) or 1 h (Sandrini *et al*., 2002) post-dose in headache intensity from moderate or severe to mild or pain-free.

Secondary end-points consisted of the following: (i) pain-free response (improvement from moderate or severe to no pain); (ii) relief of associated symptoms of nausea and photophobia/phonophobia; (iii) functional response (improvement in functional impairment from bed rest/severe impairment to some or no impairment); (iv) headache recurrence (defined as the return of a moderate to severe headache up to 24 h following a headache response at 2 h); (v) use of rescue medication; (vi) sustained response and sustained pain-free response (defined as headache response or pain-free response within 2 h of study treatment, with no subsequent headache recurrence or use of rescue medication within 24 h after the first dose of study medication); and (vii) acceptability of study medication compared with previous treatment, which was determined 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?'

Statistical analyses

The primary efficacy outcome for this combined analysis was headache response at 2 h after the first dose of study treatment. The primary efficacy comparison was between E40 and S100. In the current combined analysis, an 8% difference in response rate was considered to be a clinically meaningful difference. The combined sample size provided $>80\%$ power to detect as significant (alpha level $= 0.05$, 2-tailed) an 8% difference between eletriptan and sumatriptan in all the primary and secondary outcomes that were obtained.

Baseline characteristics of the pooled sample were compared for homogeneity across treatment groups. All efficacy analyses were performed on the intent-to-treat (ITT) sample, defined as all patients who took at least one dose of study medication and had a valid baseline and at least one post-baseline evaluation. The primary analysis was the 2-h headache responder rate for the ITT group. This analysis was conducted using a categorical linear model based on the SAS procedure CATMOD (SAS, 1989), which included terms for treatment, study and baseline severity. A treatment by study interaction term was used as a secondary term in the model to test the poolability. The interaction term was dropped from any of the above models if it was not found to be significant. Secondary end-points were analyzed by using a categorical linear model based on SAS CATMOD procedure, including treatment, study, and baseline severity.

Consistent with previous recommendations, odds ratios were calculated for important clinical outcomes (Egger *et al*., 1997; Engels *et al*., 2000). A logistic regression model was used to compare the probability of response on eletriptan versus sumatriptan. For each odds ratio, 95% confidence intervals (CIs) were calculated to provide a measure of the precision of the response probability for each outcome measure. An odds ratio >1 indicated a higher probability of treatment response with eletriptan than with sumatriptan. If the 95% CI is also >1, then one can be confident that the efficacy advantage for eletriptan over sumatriptan is true.

Results

Study sample

A total of 2906 patients in the combined sample received study treatment for a single migraine headache and had at least one post-dose assessment (ITT sample; Fig. 2). Patients in each treatment group had similar demographic and clinical characteristics (Table 1), which were typical of patients entering acute treatment studies of migraine.

Relief of headache and pain-free response

Eletriptan 40 mg showed significantly higher headache response rates versus S100 at both 1 h (34% vs. 26%; $P < 0.0001$; Fig. 3), and at 2 h (67% vs. 57%; $P < 0.0001$). Eletriptan 40 mg also showed higher

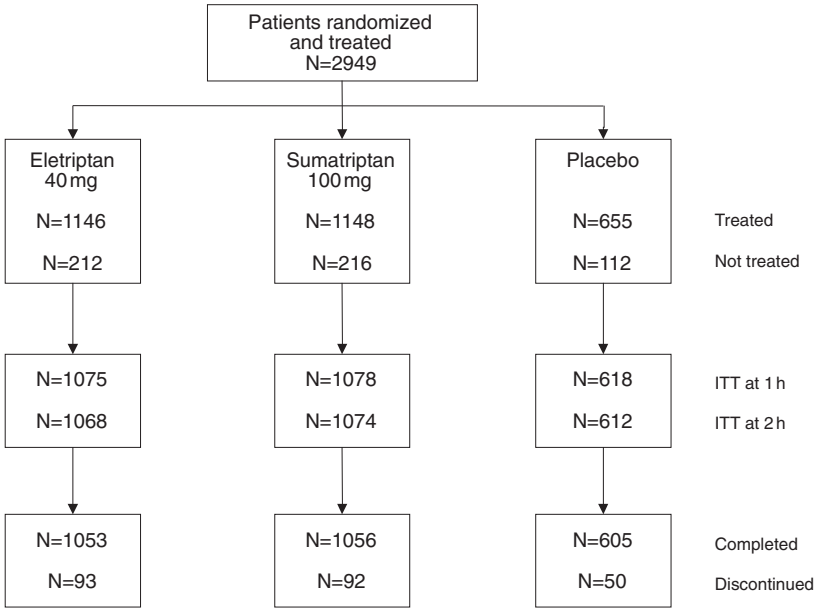

Figure 2 Disposition of patients. ITT, intent-to-treat.

Table 1 Patient demographic and clinical characteristics

	Placebo ($n = 645$)	Sumatriptan 100 mg ($n = 1129$)	Eletriptan 40 mg ($n = 1132$)
Female (%)	85	86	87
Age (years; mean ± SD)	41.1 ± 10.5	41.0 ± 10.4	40.7 ± 10.8
Range (years)	18–66	18–76	18–71
Migraine subtype (%)			
Without aura	66	66	64
With aura	13	14	16
Mixed	20	20	21
Characteristics of treated attack			
Headache rated as severe (%)	42	41	40
Incidence of associated symptoms (%)			
Nausea	65	64	63
Photophobia/phonophobia	83	84	82
Functional impairment severe (%)	27	25	27

pain-free response rates at 2 h (35%) compared with both sumatriptan (25%; $P < 0.0001$) and placebo (5%; $P < 0.0001$). The sumatriptan pain-free response rate was also significantly ($P < 0.0001$) higher than that of placebo at 2 h. Pain-free rates were significantly different from placebo (<1%; $P < 0.0001$) at 1 h for either eletriptan (7%) or sumatriptan (5%).

Relief of associated symptoms

Treatment with E40 was associated with significantly greater relief of nausea at 2 h (63%) compared with both sumatriptan (56%; $P < 0.01$) and placebo (41%; $P < 0.0001$; Fig. 4). Similarly, eletriptan provided significantly greater relief of photophobia/phonophobia (59%) than both sumatriptan (51%; $P < 0.001$) and placebo (27%; $P < 0.0001$).

Functional response

Treatment with eletriptan resulted in a rapid return to normal or near-normal levels of functioning, with significantly more patients showing a functional response at 1 h on E40 (33%) compared with both S100 (27%; $P < 0.05$) and placebo (15%; $P < 0.001$). Similarly, 67% of patients demonstrated a functional response at 2 h on eletriptan compared with 58% on sumatriptan ($P < 0.0001$) and 30% on placebo ($P < 0.0001$; Fig. 5).

Use of rescue medication and clinical outcome at 24 h post-dose

Treatment with eletriptan was associated with significantly less use of rescue medication (20%) compared with that of sumatriptan (27%; $P < 0.001$) and placebo

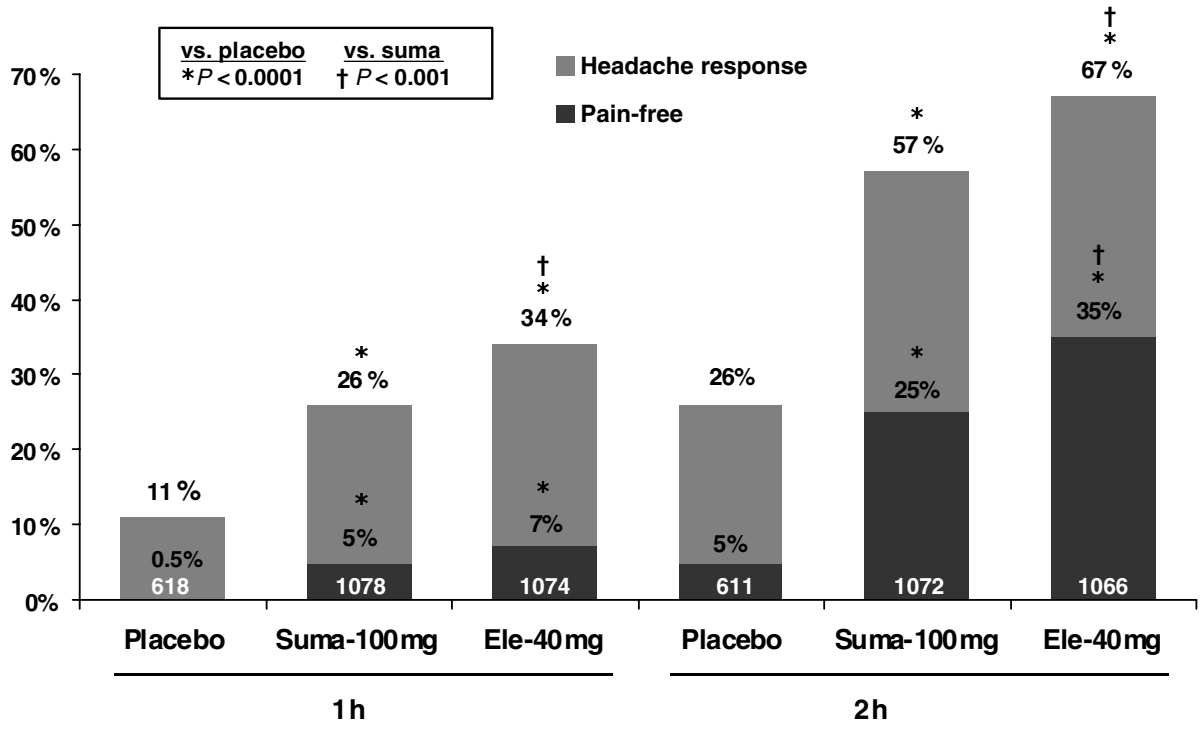

Figure 3 Headache response and pain-free response at 1 and 2 h. Suma, sumatriptan; ele, eletriptan.

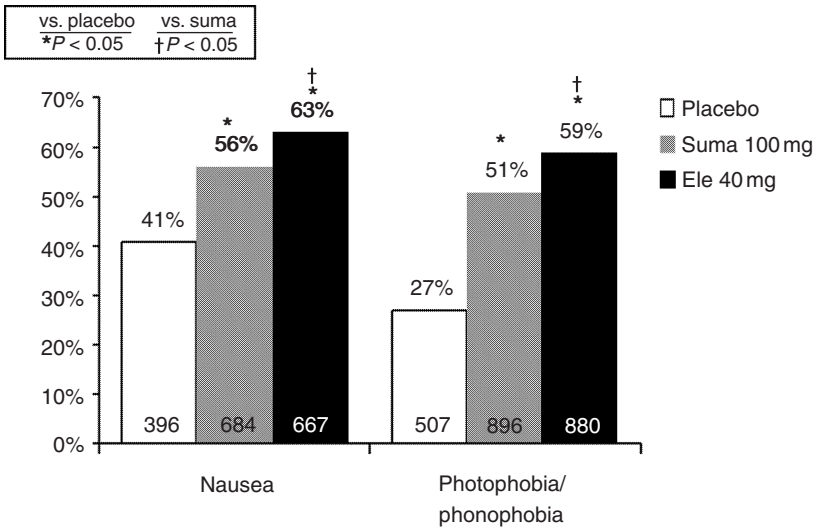

Figure 4 Relief of associated symptoms at 2 h. Suma, sumatriptan; ele, eletriptan.

(52%; $P < 0.0001$; Fig. 6). In addition, amongst patients who achieved a 2-h headache response, headache recurrence rates were significantly lower in those treated with eletriptan (29%) compared with those on sumatriptan (35%; $P < 0.05$) and placebo (39%; $P < 0.05$; Fig. 6). As a consequence, sustained headache response and pain-free rates (Fig. 7) were significantly higher in the eletriptan group (42% and 22%, respectively) compared with the sumatriptan (34%, $P < 0.0001$; and 15%, $P < 0.0001$) and placebo groups (14%, $P < 0.0001$; and 3%, $P < 0.0001$).

Eletriptan versus sumatriptan: comparative response across key clinical outcomes

Figure 8 summarizes the odds ratios for each efficacy measure based on the logistic regression. Eletriptan had significantly greater efficacy than sumatriptan across all eight clinical outcome measures, with the following mean (±95% CI) odds ratios: headache relief at 1 h, 1.48 (1.22–1.79); headache relief at 2 h, 1.50 (1.25–1.80); relief of photophobia/phonophobia at 2 h, 1.45 (1.20–1.75); relief of nausea at 2 h, 1.36 (1.09–1.69); functional

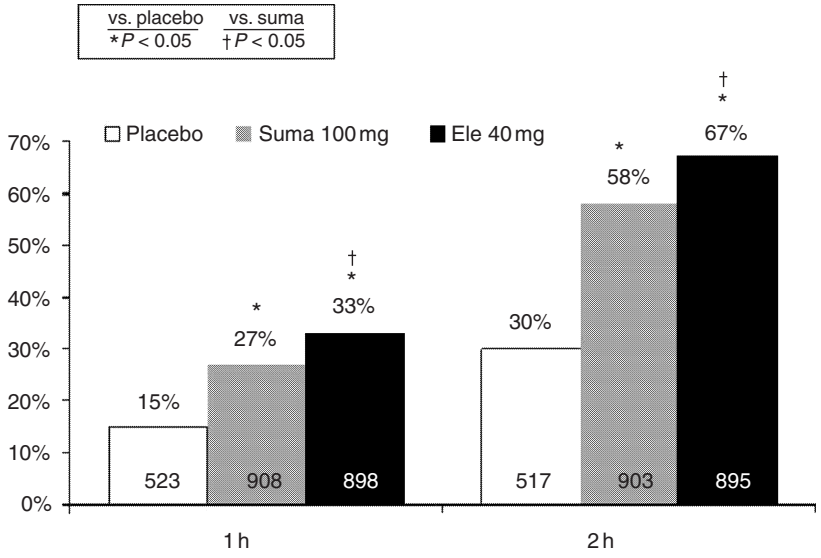

Figure 5 Functional response at 1 and 2 h. Suma, sumatriptan; ele, eletriptan.

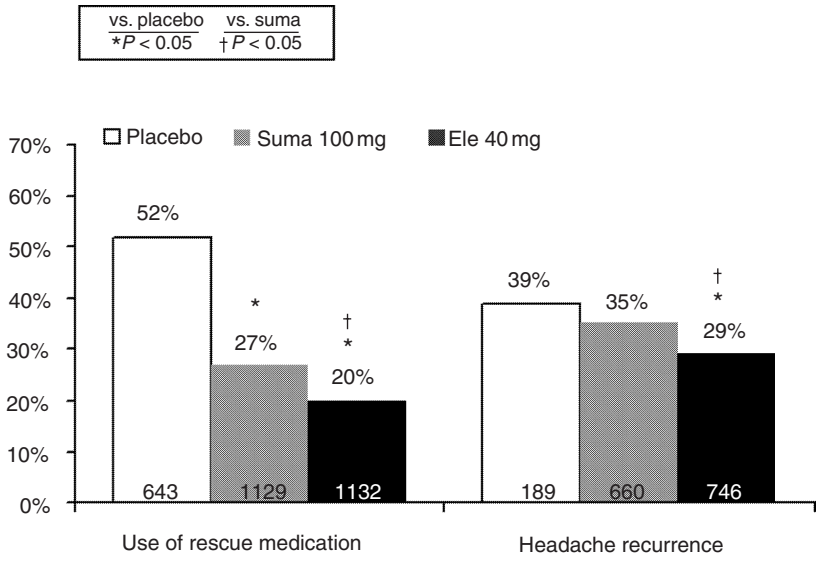

Figure 6 Use of rescue medication and headache recurrence at 24 h. Suma, sumatriptan; ele, eletriptan.

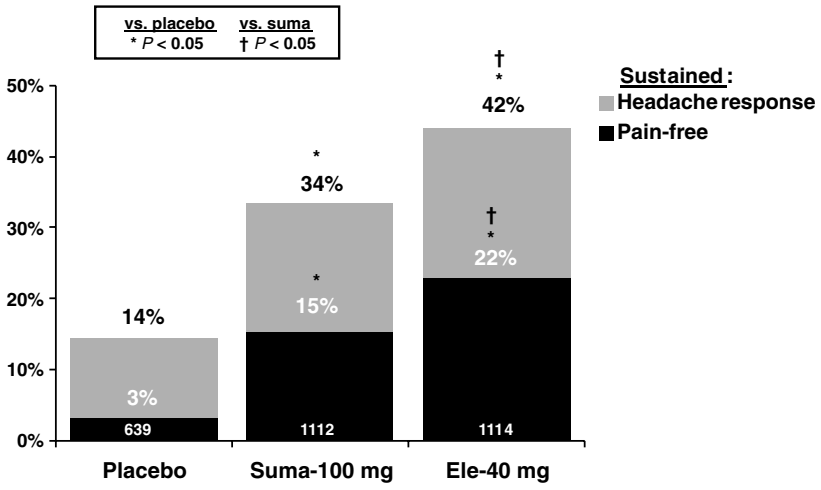

Figure 7 Sustained headache response and sustained pain-free response at 24 h. Suma, sumatriptan; ele, eletriptan.

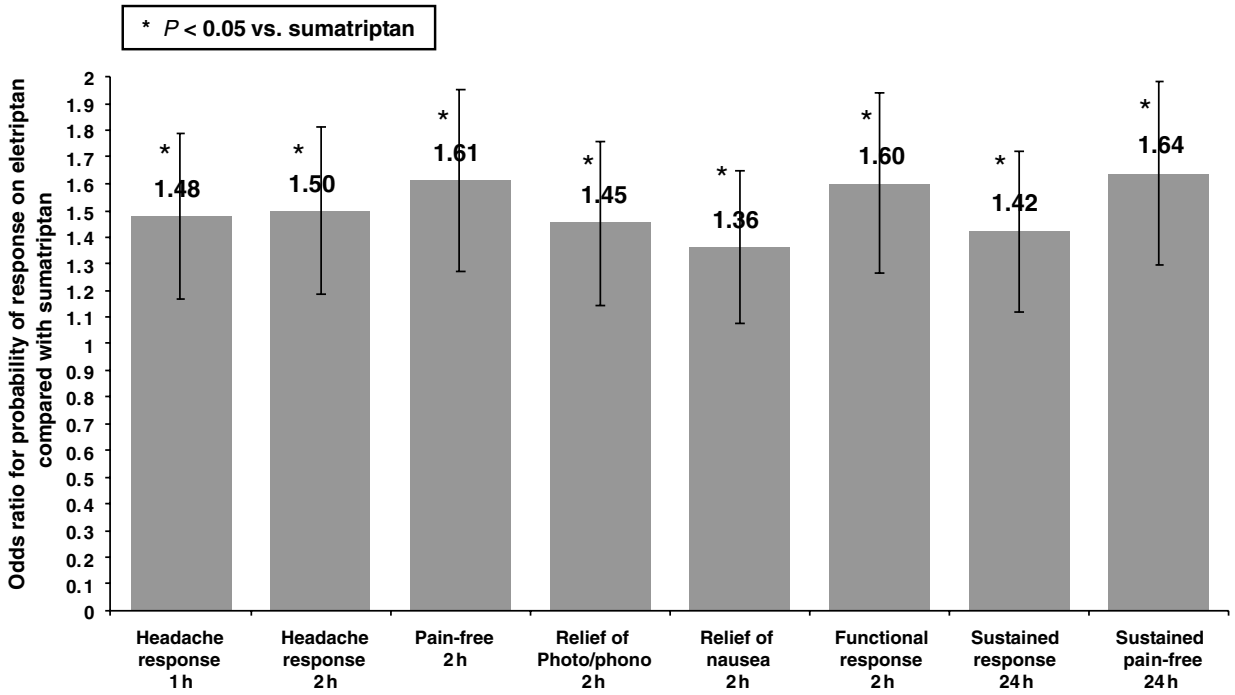

Figure 8 Odds ratios for clinical response on eletriptan 40 mg (E40) versus sumatriptan 100 mg (S100). (Note: An odds ratio of 1.48 indicates that a patient treated with E40 is 48% more probable to achieve a headache response than if the patient had been treated with S100.)

response at 2 h, 1.60 (1.31–1.95); pain-free at 2 h, 1.61 (1.33–1.94); sustained response at 24 h, 1.42 (1.19–1.68); and sustained pain-free at 24 h, 1.64 (1.32–2.04). A headache response odds ratio of 1.48 (headache response at 1 h) indicates that a patient treated with the 40-mg dose of eletriptan is 48% more probable to achieve a headache response than if the patient had been treated with the 100-mg dose of sumatriptan.

Tolerability and safety

Both eletriptan and sumatriptan were well tolerated with the majority of adverse events reported as mild and transient (Table 2). Based on the incidence and severity of adverse events summarized in Table 2, eletriptan demonstrated tolerability that was comparable with placebo in all areas except for asthenia. No serious treatment-related adverse events occurred in either the eletriptan or sumatriptan groups. No clinically significant treatment-emergent laboratory or ECG abnormalities, or changes in vital signs, were recorded.

Patient preference for migraine treatment

Patient global ratings of treatment acceptability (recorded at 24 h for current versus prior migraine treatments) were significantly higher for eletriptan (67%) versus both sumatriptan (59%; $P < 0.001$) and placebo (27%; $P < 0.0001$; Fig. 9). Sumatriptan also demonstrated significantly higher acceptability versus placebo ($P < 0.0001$).

Table 2 Incidence of treatment-emergent adverse events (AEs) (all-causality) with incidence of ≥3% in either active-treatment group

	Placebo ($n = 655$) (%)	Sumatriptan 100 mg ($n = 1148$) (%)	Eletriptan 40 mg ($n = 1146$) (%)
Asthenia	1.2	3.7	2.6
Migraine	4.3	3.0	3.1
Nausea	9.2	12.4	9.7
Vomiting	9.0	4.9	4.5
Photophobia	3.7	3.7	3.0
Proportion of patients rating any of top five AEs as 'severe'	3.1	2.6	2.0

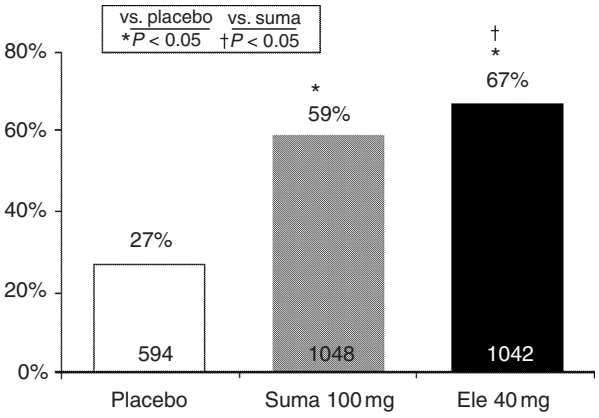

Figure 9 Treatment acceptability at 24 h (versus previous migraine treatment). Suma, sumatriptan; ele, eletriptan.

Discussion

Two of three previously reported placebo-controlled studies found the 40-mg dose of eletriptan to have significantly greater efficacy in the acute treatment of migraine than the 100-mg dose of sumatriptan (Sandrini *et al*., 2002; Mathew *et al*., 2003) (Fig. 1). The current combined analysis extends these findings, permitting a more precise estimate to be calculated of the magnitude of the efficacy advantage of eletriptan across multiple clinical outcome dimensions. The current results are based on the largest ($n = 2770$) comparator data set ever reported that directly compares two triptans in placebo-controlled trials.

The results of this combined analysis found a 10-point superiority on the primary outcome measure, headache response at 2 h (Fig. 3), in favor of eletriptan (67%, 95% CI: 64–70%) versus sumatriptan (57%, 95% CI: 54–60%). Furthermore, the addition of new placebo-controlled efficacy data on the 40-mg dose of eletriptan from the new sumatriptan trial (Mathew *et al*., 2003) and from two other triptan comparator studies (Garcia Ramos *et al*., 2003; Steiner *et al*., 2003), results in a more than twofold increase in sample size beyond what was originally reported in the meta-analysis by Ferrari *et al*. (2001).

Secondary outcome measures

The efficacy of eletriptan on all secondary outcomes in the combined analysis was consistent with the results on the primary outcome measure, with a 7–8% absolute advantage of eletriptan in relief of associated symptoms (Fig. 4), a 9% eletriptan advantage in functional response (Fig. 5), and an 8% eletriptan advantage in both sustained headache response and sustained pain-free response (Fig. 7).

Perhaps the most useful metric for evaluating the *clinical* significance (as opposed to statistical significance) of the difference in efficacy is calculation of odds ratios. Odds ratios are a standard method (Egger *et al*., 1997) for summarizing the overall likelihood of achieving response to one drug compared with another. Figure 8 shows that treatment with eletriptan is associated with a consistently and significantly higher probability of achieving a response across all important clinical outcomes in migraine. On average, treatment with eletriptan resulted in an approximately 50% higher probability of achieving a response in any given clinical outcome dimension. The probability of a favorable outcome when treated with eletriptan was particularly high for two of the most stringent outcomes: the ability to achieve a pain-free response by 2 h (61% higher than sumatriptan), and the ability to sustain the pain-free response over a full 24 h (64% higher than sumatriptan). The large sample size used in the current analysis increases our confidence that the odds ratio estimates are close estimates of true drug effect.

Results in context

A dozen studies have been reported (Dowson *et al*., 2002a; Dowson and Charlesworth, 2002b; Gallagher *et al*., 2000; Geraud *et al*., 2000; Geraud *et al*., 2002; Gobel *et al*., 2000; Goldstein *et al*., 1998; Havanka *et al*., 2000; Lines *et al*., 2001; Tfelt-Hansen *et al*., 1998, 2000; Visser *et al*., 1996) in which a newer triptan has been compared with either the 50 or 100-mg dose of sumatriptan in a double-blind, head-to-head trial. Of these studies, no previous triptan except eletriptan has been able to demonstrate significant superiority on the *a priori* primary outcome measure, headache response at 2 h. Rizatriptan, previously the best studied in head-o-head trials, has been compared in two studies of rizatriptan 10 mg versus S100 (Visser *et al*., 1996; Tfelt-Hansen *et al*., 1998), and one study of rizatriptan 10 mg versus sumatriptan 50 mg (Goldstein *et al*., 1998). In none of these studies did rizatriptan demonstrate statistical significance versus sumatriptan on the primary outcome. However, two of the studies had relatively high placebo response rates [38% (Goldstein *et al*., 1998) and 40% (Tfelt-Hansen *et al*., 1998)], which may have made it difficult to evaluate between-drug differences in efficacy because of strong non-specific treatment effects in the study samples.

Tolerability and safety

The superiority of the E40 compared with S100 raises the question of whether the efficacy advantage comes at a price of more frequent adverse events. The data in the

current analysis provide reassurance that this is not the case: the 40-mg dose of eletriptan is equal (or better) tolerated than sumatriptan (Table 2), with a tolerability profile that is comparable with placebo. Only asthenia is more frequent with eletriptan than with placebo.

Conclusion

We have presented results of an analysis of combined efficacy and tolerability data from three placebo-controlled trials of E40 versus S100 in the acute treatment of migraine. Eletriptan demonstrated consistently and significantly superior efficacy compared with sumatriptan across all clinically relevant outcomes. The choice of eletriptan to treat an acute attack was associated with a significantly higher probability of response compared with the use of sumatriptan, with an especially notable advantage in favor of eletriptan in pain-free and functional response at 2 h, and sustained pain-free response at 24 h (approximately 60% higher probability of response on all three outcomes). Treatment with E40 showed a tolerability profile that was very similar to that of placebo. The current results constitute an unusually large head-to-head comparator database upon which evidence-based treatment decisions concerning choice of triptan can be made.

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