Views and Perspectives

Tolerability and Safety of Eletriptan in the Treatment of Migraine: A Comprehensive Review

Ninan T. Mathew, MD; Jayasena Hettiarachchi, MD; Jeffrey Alderman, PhD

Objective.—To provide a comprehensive review of the tolerability and safety of eletriptan.

Background.—Eletriptan is a potent and selective 5-$HT_{1B/1D}$ agonist that has demonstrated significant efficacy in the acute treatment of migraine in doses of 20 mg, 40 mg, and 80 mg.

Design.—This review reports the tolerability and safety of eletriptan across a broad spectrum of preclinical studies and clinical trials that collectively included treatment of more than 11 000 subjects and more than 74 000 migraine attacks.

Results.—In clinical trials, eletriptan was well tolerated and safe across its dosing range of 20 mg to 80 mg. The adverse event profile of eletriptan 20 mg was similar to placebo, while the most commonly used dose, eletriptan 40 mg, has an adverse event profile that is only marginally higher than placebo. Eletriptan was safe and well tolerated regardless of age or gender, and for both short- and long-term treatment. Eletriptan is metabolized primarily by the CYP3A4 enzyme. Coadministration of potent CYP3A4 inhibitors was not associated with clinically meaningful change in eletriptan tolerability or safety in the population included in these clinical trials. The margin of cardiovascular safety for eletriptan was also confirmed by a well-controlled clinical study in which intravenous eletriptan in excess of an 80-mg dose was rapidly infused in patients undergoing coronary angiography; nonetheless, it is recommended that eletriptan not be coadministered with a limited list of 7 potent CYP3A4 inhibitors; in addition, the triptan class in general (including eletriptan) is contraindicated in patients with symptoms or findings consistent with ischemic heart disease or other significant underlying cardiovascular disease.

Conclusions.—This comprehensive review found that eletriptan is safe and well tolerated, and that relatively large changes in dose and plasma concentration result in minimal changes in tolerability.

Key words: eletriptan, sumatriptan, triptan, migraine, acute treatment, headache, safety

Abbreviations: ELE-20, ELE-40, ELE-80, ELE-160 eletriptan 20 mg, 40 mg, 80 mg, and 160 mg, respectively; PK pharmacokinetic; C_{max} maximum concentration; SSRIs selective serotonin reuptake inhibitors; OCs oral contraceptives; PD pharmacodynamic; AEs adverse events

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Eletriptan is a newer triptan that has been studied in an extensive development program that included treatment of more than 11 000 subjects and more than 74 000 migraine attacks. Eletriptan has demonstrated significant efficacy for the acute treatment of migraine across the dosage range of 20 mg (ELE-20), 40 mg (ELE-40)—the highest recommended single dose in the United States, and 80 mg (ELE-80). Table 1 provides a concise summary of the comparative efficacy of eletriptan based on 6 recently reported head-to-head comparative trials.[1-6] The significance levels for eletriptan versus placebo and eletriptan versus active comparators are shown for representative efficacy measures: ELE-40 and ELE-80 both demonstrate higher efficacy compared to other migraine-specific therapies across key clinical outcomes. Eletriptan 20 mg has efficacy similar to the 100-mg dose of sumatriptan.[1]

The safety and tolerability of eletriptan has been previously reported in the individual studies

From the Houston (Tex) Headache Clinic (Dr. Mathew) and Pfizer Inc., New York, NY (Drs. Hettiarachchi and Alderman).

Address correspondence to Dr. Ninan T. Mathew, Houston Headache Clinic, Suite 350, 1213 Hermann Drive, Houston, TX 77004 and reprint requests to Dr. Jayasena Hettiarachchi, Pfizer Inc., 235 East 42nd Street, New York, NY 10017.

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Table 1.—Summary of Comparative Efficacy of Eletriptan*

Comparative Study, y	Headache Response at 2 Hours	Pain-free Response at 2 Hours	Functional Response at 2 Hours	No Nausea at 2 Hours	Sustained Response at 24 Hours
Goadsby et al,[1] 2000					
Eletriptan 20 mg	54†	19†	53†	67†	33
Eletriptan 40 mg	65†	29†	64†,‡	64†	38†
Eletriptan 80 mg	77†,‡	37†,‡	75†,‡	75†	42†
Sumatriptan 100 mg	55†	23†	52†	62†	32†
Sandrini et al,[2] 2002					
Eletriptan 40 mg	64†,‡	31†,‡	63†,‡	71†,‡	50†,‡
Eletriptan 80 mg	67†,‡	37†,‡	55†,‡	65†	54†,‡
Sumatriptan 50 mg	50†	19†	46†	60†	34†
Sumatriptan 100 mg	53†	18†	46†	58†	38†
Mathew et al,[3] 2003					
Eletriptan 40 mg	67†,‡	36†,‡	68†,‡	74†,‡	43†,‡
Sumatriptan 100 mg	59†	27†	61†	67†	34†
Diener et al,[4] 2002					
Eletriptan 40 mg	54†,‡	28†,‡	52†,‡	62†,‡	40†,‡
Eletriptan 80 mg	68†,‡	38†,‡	62†,‡	62†,‡	51†,‡
Cafergot	33†	10†	31†	34†	27†
Garcia-Ramos et al,[5] in press					
Eletriptan 40 mg	56†,‡	35†,‡	60†,‡	73	38†,‡
Naratriptan 2.5 mg	42†	18†	52†	68	27
Steiner et al,[6] in press					
Eletriptan 40 mg	64†	32†	61†	72†,‡	44†,‡
Eletriptan 80 mg	74†,‡	44†,‡	68†,‡	72†,‡	47†,‡
Zolmitriptan 2.5 mg	60†	26†	56†	64†	35†

*Values are percentages.
†$P < .05$, study drug versus placebo.
‡$P < .05$, eletriptan versus active comparator.

summarized in Table 1, but no comprehensive review summarizes its overall tolerability and safety; that is the purpose of this report. Because pharmacologic and pharmacokinetic (PK) information are important for understanding the tolerability and safety profile of eletriptan, these 2 topics are reviewed briefly first.

Marketed triptans, including eletriptan, are notable for their potent and highly selective affinity (pKi = 8 to 9) for 5-HT_{1B}, and 5-HT_{1D} (and 5-HT_{1F}) receptors, which have been implicated in the pathophysiology of migraine.[7] Eletriptan has no clinically meaningful activity at any other pharmacologic targets (eg, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_6, α_1, α_2, or β-adrenoceptors; adenosine A_1, dopamine D_1 or D_2, muscarinic, histaminic).[7] This lack of affinity at other receptors is the pharmacologic basis for the high degree of safety and tolerability of the triptan class.

Eletriptan Pharmacokinetics.—After oral dosing, absorption from the gastrointestinal (GI) tract is rapid, with an absolute bioavailability of about 50%. The mean time to maximum concentration (T_{max}) is about 1.5 hours after dosing in healthy volunteers, and the median is 2.0 hours during an acute migraine attack. Pharmacokinetics are linear over the clinical dose range. The terminal elimination half-life ($t_{1/2}$) is approximately 4 hours. Eletriptan is moderately protein bound (85%). Approximately 90% of clearance is nonrenal, indicating that eletriptan is eliminated primarily by metabolism. The volume of distribution is 138 L (after intravenous [IV] dosing) and the mean clearance is 36 L per hour. The PK parameters of eletriptan

Table 2.—Drug Interaction Study: Coadministration With Ketoconazole (a High Potency CYP3A4 Inhibitor)*

Parameter	Eletriptan 80 mg + Placebo (n = 18)	Eletriptan 80 mg + Ketoconazole 400 mg (n = 18)	Mean Ratio (Inhibitor/Placebo)	95% Confidence Interval
C_{max}, ng/mL	177.7	474	2.67	2.29-3.10
AUC, ng/h/mL	1190	7029	5.91	5.16-6.76
$t_{1/2}$, h	4.75	8.29	—	—

*C_{max} indicates maximum concentration; AUC, area under the curve; $t_{1/2}$, half-life.

are unaffected by age, gender, race, or time in the menstrual cycle.[8]

Eletriptan is primarily metabolized by the CYP3A4 enzyme, with a small contribution (less than 10%) from other CYP enzymes. The *N*-demethylated metabolite, the only known active metabolite of eletriptan, has plasma concentrations that are 10% to 20% of those of the parent drug. Eletriptan does not inhibit or induce any CYP enzymes and, therefore, is unlikely to cause clinically important interactions or to alter the plasma levels of other drugs.

In a CYP3A4 interaction study with the potent inhibitor, ketoconazole, coadministration was associated with a 2.7-fold increase in eletriptan's maximum concentration (C_{max}) and a 6-fold increase in the area under the curve (AUC) (Table 2). Ketoconazole was utilized at the highest recommended daily dose of 400 mg per day to test the maximum effect of potent CYP3A4 inhibition on the plasma concentration of the highest dose (80 mg) of eletriptan. Eletriptan also has been studied in a series of other drug interaction studies to evaluate the effects of a range of mild and moderate CYP3A4 inhibitors including fluconazole, erythromycin, and verapamil on PK parameters. As expected, compared to the potent CYP3A4 inhibitor, ketoconazole, all yielded lesser increases in both C_{max} and AUC. Taken together, these results indicate that concomitant use of eletriptan with CYP3A4 inhibitors is associated with predictable increases in C_{max} (based on 50% bioavailability), up to a maximum 2- to 3-fold increase with the most potent inhibitors.

METHODOLOGY

This review of eletriptan tolerability and safety will focus on the following clinically important topics: (1) tolerability in short-term randomized trials; (2) tolerability and safety of eletriptan during long-term treatment; (3) effect of concomitant treatment with CYP3A4 inhibitors on tolerability and safety; (4) effect on tolerability and safety of concomitant treatment with other commonly used medications such as selective serotonin reuptake inhibitors (SSRIs), oral contraceptives (OCs), and hormone replacement therapy (HRT); (5) tolerability and safety of eletriptan in special populations including elderly patients, adolescents, and patients with hepatic/renal impairment; and (6) cardiovascular safety margin of eletriptan in terms of both electrocardiogram (ECG) and vital signs, and effects on coronary arteries.

The basis for this review of eletriptan's tolerability and safety includes data from 42 clinical pharmacology studies. Among these, 23 studies included pharmacodynamic (PD) assessments and 23 measured PKs of eletriptan, alone or in the presence of other drugs (some studies provided both PK and PD assessments). The clinical pharmacology studies permitted concurrent monitoring of key cardiovascular parameters such as ECG, blood pressure (BP), and in 2 studies, coronary artery diameter. The core of the eletriptan development program consisted of phase 2 and 3 placebo-controlled trials and phase 2 and 3 comparative trials. For phase 2 and 3 clinical trials, primary reports are either published or are placebo-controlled trial results in the process of being published; they include head-to-head comparative studies versus sumatriptan, Cafergot, naratriptan, and zolmitriptan.

In almost all eletriptan trials, patients recorded in their diaries adverse events (AEs), together with quantitative evaluations of severity and duration, as they occurred. Diary recording for AEs continued for up

to 7 days postdosing. This procedure may differ from other acute migraine treatment studies in which AEs are ascertained by means of retrospective assessment at the posttreatment visit. Attributions of severity and causation were made at follow-up by investigators.

RESULTS

Demographic and clinical characteristics of the patients enrolled in the clinical trials discussed here indicate that they are fairly representative of migraineurs in the community; patients were predominantly women in the age range of 30 to 50 years (Table 3).[9] Approximately one half of the patients reported another current medical diagnosis, and approximately three fourths were being treated with another medication. Table 3 lists the most common categories of concomitant medications for comorbid disorders, and indicates an expected pattern of therapy for an outpatient population in this age range.

Tolerability of Short-term Treatment in Phase 2 and 3 Clinical Trials.—The incidence of all-causality AEs, by initial dose, in short-term, randomized treatment studies is summarized in Table 4. As shown, the most commonly used dose, ELE-40, has an AE profile that is only marginally higher than placebo, with no AE occurring at a rate more than 2% higher than placebo. The pattern for AEs on the lower eletriptan dose, ELE-20, is similar to placebo, while the higher dose, ELE-80, shows modest dose-related increases in individual AEs.

Tolerability of Titration From Eletriptan 40 mg to Eletriptan 80 mg.—In the eletriptan clinical program, ELE-40 was the most common dose, providing headache relief to the majority of patients. The effect of dose titration from ELE-40 to ELE-80 was also examined in pooled data from 2 long-term treatment studies; this data illustrates the tolerability of eletriptan in patients previously exposed to at least 3 doses of ELE-40. Figure 1 summarizes the total incidence of AEs in patients on ELE-40 who elected to titrate to ELE-80 after 3 attacks. In these studies, titration was not associated with a clinically meaningful increase in AEs, indicating the extent to which ELE-40 has a high margin of tolerability. This high tolerability margin for the 40-mg dose is also illustrated by data from patients who took either ELE-80 (N = 2554) or

Table 3.—Patient Demographics and Clinical Characteristics*

Feature	Eletriptan (N = 6954)		Placebo (N = 1376)		Comparator (N = 2249)	
	Men	Women	Men	Women	Men	Women
Gender	15.6	84.4	17.7	82.3	16.2	83.8
Age, mean, y	38.3	39.7	34.9	38.6	37.9	38.9
Range	11-78	12-75	12-65	12-69	12-76	12-80
Race						
White	93.0	94.4	91.4	93.4	87.4	90.3
Other	7.0	5.6	8.6	6.6	2.6	9.7
Current concomitant illness	51.4		47.6		44.6	
Hypertension	3.3		2.5		3.3	
Concomitant medication	78.1		83.2		73.2	
Beta-blocker	9.1		8.2		8.1	
Antidepressant	13.2		10.5		8.5	
Hypnotic/anxiolytic	6.1		5.8		6.1	
Antibiotic	7.8		5.5		8.0	
Hormone replacement therapy	14.7†		13.2†		12.5†	
Oral contraceptive	19.7†		19.8†		21.1†	
Analgesic	26.8		36.8		28.4	
Antihypertensive	4.0		2.4		3.7	
Lipid-lowering drug	1.0		0.5		0.8	

*Values are percentages unless otherwise indicated.
†Percentages of women taking oral contraceptives and harmone replacement therapy.

Table 4.—Incidence of Adverse Events on Eletriptan in Short-term Clinical Trials*

Adverse Event	Placebo (n = 1559)	Eletriptan 20 mg (n = 536)	Eletriptan 40 mg (n = 2951)	Eletriptan 80 mg (n = 2085)
Paresthesias	1	3	3	4
Flushing/feeling of warmth	2	2	2	3
Chest tightness/pain/pressure	1	1	2	5
Dry mouth	2	2	3	4
Nausea	8	5	7	10
Dizziness	3	3	5	7
Somnolence	3	3	5	6
Headache	3	3	3	4
Hypertonia†	0	2	1	3
Asthenia	3	4	5	12

*Values are percentages. All causality ≥3%.
†Muscle tension and related symptoms.

ELE-160 (N = 427) to treat a single attack during clinical trials. In these 2 high-dose treatment groups, the proportion of patients who reported discontinuations due to AEs was similar (ELE-80, 2.0% versus ELE-160, 0.7%), and the incidence of severe AEs was comparable (ELE-80, 7.0% versus ELE-160, 6.3%). Although high-dose data provide reassurance about the margin of safety of eletriptan, the 40-mg dose is still the highest recommended single dose in the United States as well as some other countries.

Tolerability and Safety of Long-term Treatment With Eletriptan.—The tolerability of ELE-40 and ELE-80 was assessed during long-term treatment (up to 1 year) that encompassed more than 60 000 treated attacks in 1544 patients. An additional 371 patients were randomized to parallel treatment with flexible doses of physician's choice treatment (88% received sumatriptan in this group). An analysis of the incidence of AEs per attack (Table 5) found only the following AEs occurred at a rate higher than 2% (all causality): asthenia (ELE-40, 3.3% versus ELE-80, 2.0% versus

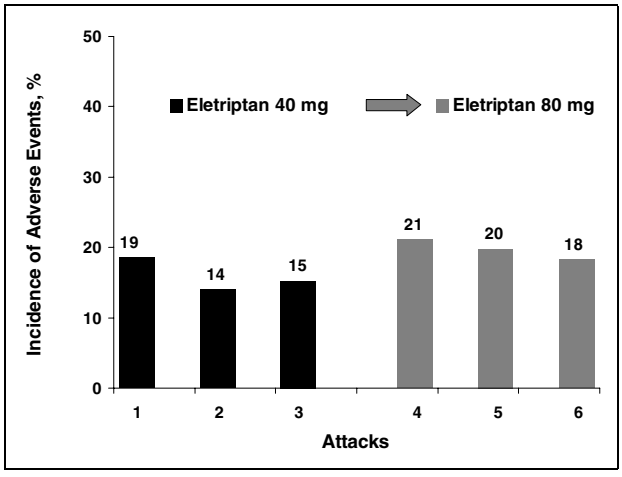

Fig 1.—Total incidence of treatment-related adverse events during titration to eletriptan 80 mg after 3 doses of eletriptan 40 mg.

Table 5.— Incidence per Attack of Adverse Events on Eletriptan in Long-term Clinical Trials*

Adverse Event	Eletriptan 40 mg	Eletriptan 80 mg	Physician's Choice Prescription†
Asthenia	3.3	2.0	1.8
Somnolence	2.9	2.6	2.2
Nausea	1.4	1.1	1.1
Chest symptoms	0.9	0.8	1.1
Dysphagia	0.9	1.3	1.8
Dizziness	0.8	1.1	0.8
Paresthesias	0.4	0.5	1.2
Hypertonia‡	0.4	1.2	0.2

*Values are percentages. All causality ≥1%.
†For patients randomized to this treatment group, physicians were permitted to treat with flexible doses of any available drug for migraine, and to change to a new drug to further optimize response.
‡Muscle tension and related symptoms.

physician's choice, 1.8%) and somnolence (ELE-40, 2.9% versus ELE-80, 2.6% versus physician's choice, 2.2%). Chest symptoms (combining pain, pressure, tightness, and related descriptors) occurred in 0.9% of attacks on ELE-40, 0.8% on ELE-80, and 1.1% on physician's choice treatment. The overall tolerability of both ELE-40 and ELE-80 was similar to that reported in patients who had been randomized to receive physician's choice treatment (Table 5).

Overall, there was only one serious AE during long-term treatment on eletriptan, characterized by a spontaneously resolving episode of bilateral clumsiness and hand weakness in a 45-year-old woman; this incident was diagnosed as a probable transient ischemic attack categorized by the investigator as related to eletriptan. During the course of long-term trials, clinically significant laboratory abnormalities were infrequent and transient, with no difference in incidence for patients treated with eletriptan or placebo.

Eletriptan and CYP3A4 Inhibitors: Effect on Tolerability.—In the United States, it is recommended that eletriptan should not be used within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir; drugs approved in the future whose label indicates similarly potent CYP3A4 inhibition may be added to this list. The potential effect of coadministration of one of these particular CYP3A4 inhibitors on the tolerability of eletriptan was evaluated during the eletriptan clinical development program. The long-term treatment studies summarized previously provide data on patients who were taking concomitant CYP3A4 inhibitors for some attacks, but not for others. The ability of patients to serve as their own controls makes this a particularly sensitive assessment of the potential effect of CYP3A4 drug-to-drug interactions on the tolerability of eletriptan. As seen in Figure 2, coadministration of potent CYP3A4 inhibitors was not associated with a clinically meaningful increase in either the total incidence of AEs or in the incidence of severe AEs. (Note that only data on use of potent inhibitors with ELE-80 are shown in Figure 2 because an insufficient number of patients [n = 16] were available for analysis of ELE-40.) The lack of any meaningful

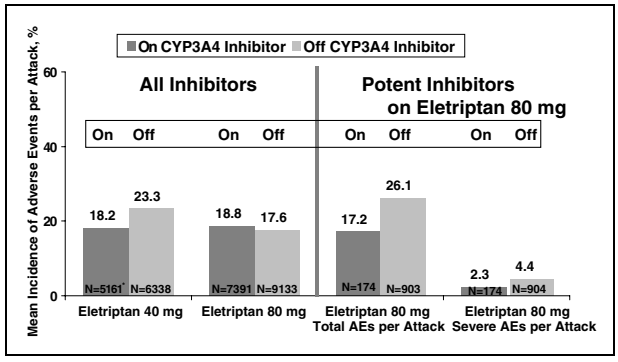

Fig 2.—Concomitant treatment with CYP3A4 inhibitors (those not recommended for use with eletriptan: ketoconazole, nefazodone, clarithromycin, itraconazole, nelfinavir, ritonavir, and troleandomycin) does not increase adverse event (AE) rates: same-patient comparison data. N = treated attacks.

effect on tolerability was true regardless of whether the CYP3A4 inhibitor was classified as potent or not. For the combined eletriptan doses, there were only 3 AEs that occurred at a per-attack rate of 2% or higher for ELE plus CYP3A4 compared to ELE alone: asthenia, 3.3% versus 2.4%; dysphagia, 2.4% versus 1.2%; and somnolence, 2.6% versus 2.3%.

Eletriptan, Oral Contraceptives, and Hormone Replacement Therapy: Effect on Tolerability.—Because of the high rate of triptan treatment among women of childbearing potential, it is important to evaluate the tolerability and safety of eletriptan during concomitant use of OCs. As shown in Table 3, 19.7% of women on eletriptan in the clinical trials database were taking concomitant OCs. Table 6 shows the results of an analysis of the incidence of AEs in women who were on OCs (versus those who were not) at the time of acute treatment with eletriptan (or placebo). The concomitant medication group also includes a small number of women who were postmenopausal taking HRT. As can be seen, concomitant administration of OC/HRT with eletriptan was not associated with any clinically meaningful increase in the incidence of or discontinuations due to AEs.

Eletriptan and Safety: Use in Special Populations.—Eletriptan was studied in 12 patients with chronic stable cirrhosis with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. There was an 18% increase in C_{max} and a 34% increase in AUC. The $t_{1/2}$ was prolonged by a mean

Table 6.—Incidence of Adverse Events on Eletriptan With and Without Concomitant Oral Contraceptives (OC) or Hormone Replacement Therapy (HRT) Versus Placebo*

Adverse Event	Eletriptan (n = 2752)	Eletriptan + OC/HRT (n = 1149)	Placebo (n = 593)	Placebo + OC/HRT (n = 209)
Discontinued due to adverse events	1.4	1.5	1.2	1.0
Asthenia	7.0	8.7	3.0	2.9
Dizziness	6.8	6.2	3.4	2.9
Somnolence	5.7	7.6	4.0	4.3
Headache	3.6	4.5	2.7	2.4
Paresthesias	3.2	4.4	1.7	1.4
Chest pain	3.0	3.1	0.8	1.4
Dry mouth	2.9	3.6	2.9	1.9

*Values are percentages. All causality ≥3% in eletriptan treatment groups and less than placebo.

of 66 minutes. (No subjects with severe hepatic impairment were studied.) Eletriptan was also studied in 16 patients with renal impairment (6 with mild impairment, creatinine clearance, 61 to 89 mL/min; 5 with moderate impairment, creatinine clearance, 31 to 60 mL/min; and 5 with severe impairment, creatinine clearance, less than 30 mL/min). Regardless of the severity of renal impairment, there was no alteration in any PK parameters. There was a modest increase in BP in patients with all degrees of renal impairment. The mean maximum increase in diastolic BP was 3.0 mm Hg in healthy volunteers, compared with 16.8 mm Hg in patients with mild renal impairment, 14.2 mm Hg in those with moderate impairment, and 17.0 mm Hg in severe renal impairment.

The incidence of AEs on eletriptan was similar across all age groups. Notably, there was no increase in the incidence of chest pain with increasing age; none of the 50 patients aged over 65 years reported this symptom.

Eletriptan is not indicated for use in children under aged 18 years, but the safety of ELE-40 has been evaluated in this population (N = 141). On ELE-40, 28% of patients reported treatment-related AEs compared to 19% on placebo. The incidence of AEs in this younger patient population was similar to that reported in adults.

Eletriptan and Selective Serotonin Reuptake Inhibitors: Effect on Tolerability.—As shown in Table 3, 13.2% of patients treated with eletriptan were taking a concurrent antidepressant. This is consistent with the high rates of comorbid affective illness reported among migraineurs, especially those with aura subtype.[10] Table 7 shows the results of an analysis of the incidence of AEs in patients treated with eletriptan (or placebo) who were on concurrent SSRI therapy. As can be seen, concomitant administration of an SSRI for patients on eletriptan was not associated with any clinically meaningful increase in the incidence of AEs or in discontinuations due to AEs. No case of serotonin syndrome was reported in the clinical program.

Eletriptan and Cardiovascular Safety.—No serious treatment-related cardiac arrhythmias, myocardial infarction, or sudden unexpected cardiac deaths occurred during the eletriptan clinical program. Because the incidence of serious cardiovascular events was below the detection threshold for a program with more than 11 000 subjects, PD studies were utilized to probe the effect of eletriptan on key cardiovascular parameters.

The effect of eletriptan on arterial blood vessels is the only clinically meaningful PD effect of this and other triptans and, therefore, to confirm the margin of safety of eletriptan (especially when coadministered with potent CYP3A4 inhibitors), it is important to establish the extent of the effects of eletriptan on coronary blood vessels at high plasma concentrations.

Table 7.—Incidence of Adverse Events on Eletriptan With and Without Concomitant Selective Serotonin Reuptake Inhibitors (SSRI) Versus Placebo*

Adverse Event	Eletriptan (n = 3908)	Eletriptan + SSRI (n = 253)	Placebo (n = 749)	Placebo + SSRI (n = 36)
Discontinued due to adverse events	1.5	1.2	1.3	0
Asthenia	7.8	4.3	2.5	2.8
Chest pain	3.1	2.8	0.9	0
Headache	3.9	2.8	2.8	8.3
Vasodilation	2.5	3.2	1.6	0
Dry mouth	3.3	3.2	2.1	2.8
Dysphagia	2.0	3.2	0.3	0
Nausea	6.7	6.3	5.3	5.6
Dizziness	6.4	7.1	3.1	0
Paresthesia	3.7	1.6	1.3	0
Somnolence	6.0	7.5	3.3	8.3

*Values are percentages. All causality ≥3% in one of eletriptan treatment groups.

Mild and transient increases in BP and similarly mild and transient effects on coronary artery tone (typically within the physiological range) are well-characterized effects of triptans. For this reason, eletriptan, along with other triptans, has class labeling contraindicating its use in patients with clinically significant cardiovascular disease, specifically ischemic heart disease and uncontrolled hypertension. It is strongly recommended that triptans, including eletriptan, not be given to patients with risk factors for coronary artery disease without a cardiovascular evaluation.

The vasoconstrictive effect of triptans is mediated by their selective activity at 5-HT_{1B} receptors. Fortunately, regulation of coronary arterial vasomotor tone is only weakly (less than 25%) under the control of 5-HT_{1B} receptors.[11-18] This suggests that in healthy coronary arteries even high concentrations of triptans will be associated with only modest vasoconstrictive effects. A series of in vitro (preclinical) and in vivo (clinical) studies have confirmed the minimal effect of eletriptan, even at extremely high concentrations, on coronary artery tone. An in vitro study of healthy human arteries found that eletriptan had an 86-fold selectivity for cranial versus coronary artery constriction (Figure 3).[19] Sumatriptan, conversely, exhibited a 30-fold selectivity for cranial versus coronary artery constriction. Even at concentrations more than 3-fold higher than the C_{max} of ELE-80, eletriptan resulted in only small concentration-related decreases in coronary artery diameter (Figure 3).

To confirm these preclinical results, angiograms were performed on patients undergoing cardiac evaluation of chest pain.[20] Patients who had normal coronary arteries were challenged with one of the following 3 treatments: (1) high-dose IV eletriptan (to a concentration 3 to 5 times above the maximum achieved

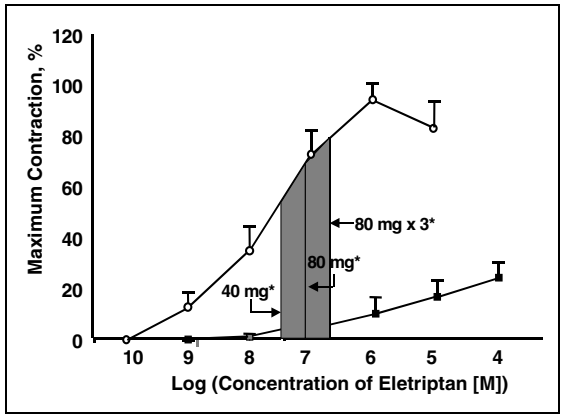

Fig 3.—In human arteries (tested in vitro) eletriptan selectively constricts cranial arteries (open circles) associated with migraine, but only minimally constricts coronary arteries (filled squares) (less than 10% even at plasma concentrations 3 times maximum concentration [C_{max}]). Vertical lines indicate C_{max} plasma levels achieved by oral doses of eletriptan: 40 mg, 80 mg, and 240 mg (80 mg times 3).[19]

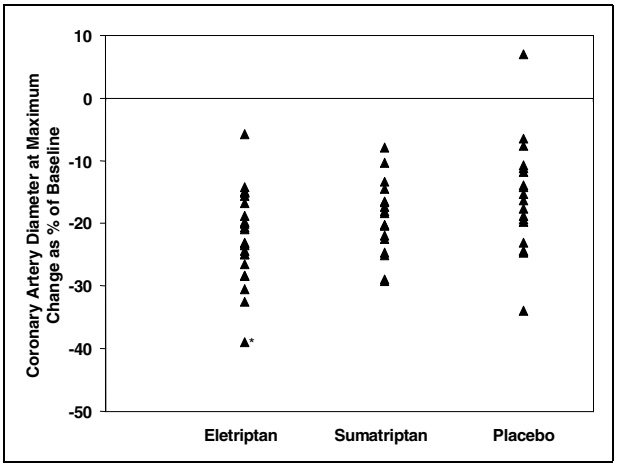

Fig 4.—Maximum percentage change in left anterior descending coronary artery diameter: comparison of high-dose intravenous eletriptan versus sumatriptan (6 mg subcutaneous) versus placebo. *Protocol violator with congenital coronary anatomic anomaly before study entry.

by oral doses of ELE-80; n = 24); (2) standard therapeutic doses of sumatriptan (6 mg subcutaneous [SQ]; n = 18); and (3) placebo (n = 18). Mean maximum changes in coronary artery diameter of 15% to 22% were observed in all 3 groups, which is within the normal physiological range.[21] No cases of clinically significant vasoconstriction were observed. Furthermore, IV eletriptan was associated with only small dose-related decreases in coronary artery diameter, similar to those seen with the standard 6-mg dose of SQ sumatriptan (Figure 4). As seen in Figure 5, the degree of dose- and concentration-related reduction in coronary artery diameter for patients on eletriptan was very modest. The vertical guideline in Figure 5 at approximately 450 ng/mL represents the maximal plasma concentration observed when ELE-80 was coadministered in a drug interaction study with the potent CYP3A4 inhibitor, ketoconazole. As illustrated, the majority of the patients achieved eletriptan blood levels that were higher than the anticipated C_{max} after an 80-mg dose of eletriptan administered with a potent CYP3A4 inhibitor. Taken together, these findings indicate that eletriptan has a high margin of cardiovascular safety in patients without coronary artery disease.

In a previous, uncontrolled, pilot angiography study of intravenously infused eletriptan,[22] one patient with a history of angina, hypertension, and hypercholesterolemia experienced chest tightness, confirmed to be a segmental coronary artery constriction, but with no associated ischemic ECG changes. It was unclear whether this event was due to eletriptan (C_{max} of 127 ng/mL, equivalent to a 60-mg oral dose), or whether it was catheter-induced as noted by the investigators.

Eletriptan and Safety: Effects on Electrocardiogram and Vital Signs.—The triptan class has not been reported to prolong the corrected QT interval (QTc) or to have any clinically significant effects on cardiac conduction. Consistent with this, eletriptan was found to have no effect on the QTc or other cardiac conduction parameters based on the following 4 categories

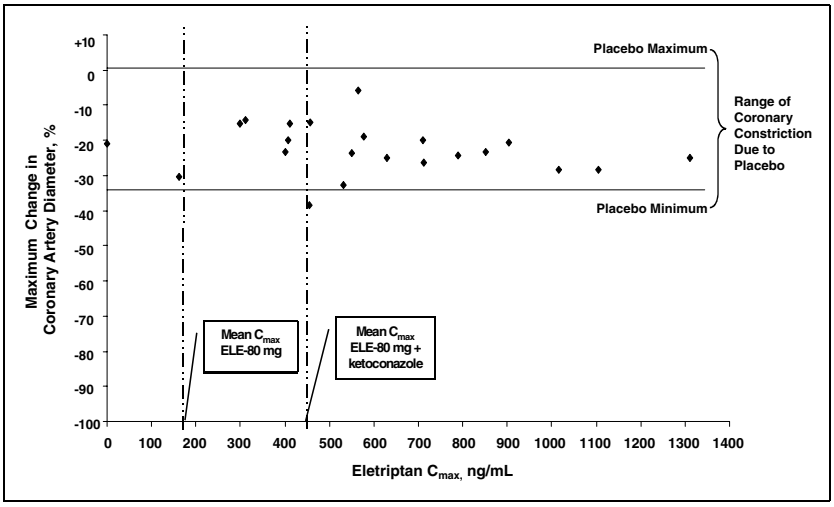

Fig 5.—Lack of correlation between maximum eletriptan (ELE-80) plasma concentration (C_{max}) and maximum change in coronary artery diameter (mid left anterior descending).

of evidence: (1) no effect on ECG when administered in very high doses in vivo in animals; (2) no effect on ECG during concurrent monitoring in PD studies of 56 healthy volunteers who were administered doses of eletriptan up to 120 mg; (3) no clinically meaningful effect on ECG parameters when assessments were made posttreatment in clinical trials (eg, the proportion of patients with a QTc prolongation longer than 60 msec was lower on eletriptan [1.2%] versus placebo [1.6%]); and (4) no serious treatment-related cardiac arrhythmias or sudden unexpected cardiac deaths occurred during the eletriptan clinical program.

Increases in BP are a commonly reported triptan class effect related to their pharmacological effects. The dose-effect curve for BP and heart rate for eletriptan was evaluated using 3 clinical data sets: (1) concurrent monitoring of BP and heart rate across clinical pharmacology studies, (2) concurrent monitoring of BP and heart rate in drug interaction studies, and (3) monitoring of BP and heart rate during the high-dose eletriptan angiography study (summarized in a previous section). The concentration-effect curve for both systolic and diastolic BP was very flat, with substantial scatter and only a very weak correlation between C_{max} and BP. Based on both linear and nonlinear (maximal effect [E_{max}]) model fitting, the effect of eletriptan on BP reached an asymptote at approximately 10 mm Hg, above which further increases in concentration had very little additional effect.

Eletriptan and Safety: Other Safety Parameters.— Across the safety database, there were no clinically significant differences in treatment-emergent laboratory test abnormalities, including liver function tests attributed to eletriptan versus placebo (Table 8). This was true for both the clinical trials database, as well as clinical pharmacology studies, in which laboratory testing was performed closer in time to actual dosing.

The incidence of discontinuations due to treatment-related AEs or laboratory abnormalities was 2.2% on eletriptan, 0.8% on placebo, and 0.7% on active comparative drugs. In the total clinical trials database of more than 11 000 patients receiving oral eletriptan, there were no cases of myocardial infarction. Only 5 patients experienced serious adverse events considered possibly or probably related to eletriptan, including 1 incidental finding of a transient increase in liver enzymes that resolved spontaneously; 1 case of bilateral clumsiness and hand weakness in a 45-year-old woman that spontaneously resolved in a few minutes; 1 case of transient difficulty in speech during the aura phase in a patient with history of similar episodes; 1 case of cerebral hemorrhage leading to death (but in a patient with no evidence of ingestion of eletriptan and no detectable eletriptan in postmortem tissues); and 1 case of atrial fibrillation in a patient with history of atrial fibrillation.

Table 8.—Incidence of Clinically Significant Liver Function Abnormalities Across All Clinical Trials*

Liver Function Abnormality	Eletriptan (n = 6577–6739)	Placebo (n = 512)
Total bilirubin increase	0.7	1.4
Aspartate aminotransferase (SGOT) increase	0.3	0.4
Alanine aminotransferase (SGPT) increase	0.5	0.2

*Values are percentages.

Comparative Efficacy of Eletriptan: Efficacy Side of the Efficacy/Tolerability Equation.—The efficacy of ELE-20, ELE-40 (highest recommended dose in United States), and ELE-80 have been evaluated in a series of head-to-head comparative trials versus sumatriptan 100 mg (3 studies), Cafergot (1 study), naratriptan 2.5 mg (1 study), and zolmitriptan 2.5 mg (1 study). The results for headache response at 2 hours are shown in Table 1. Eletriptan 40 mg demonstrated high efficacy compared to other migraine-specific therapies, and significantly superior efficacy compared in 2 trials with sumatriptan 100 mg, and separate trials with naratriptan and Cafergot. Treatment with ELE-80 was associated with approximately a 10-point additional efficacy advantage when compared to ELE-40.

Patient Acceptability: Integrating Efficacy and Tolerability.—Patient acceptability of a drug, compared to previous migraine treatments, is used as an index of a patient's integrated subjective experience. It combines components of both efficacy and tolerability, then compares this overall impression to previous treatments. Patient acceptability ratings are shown in

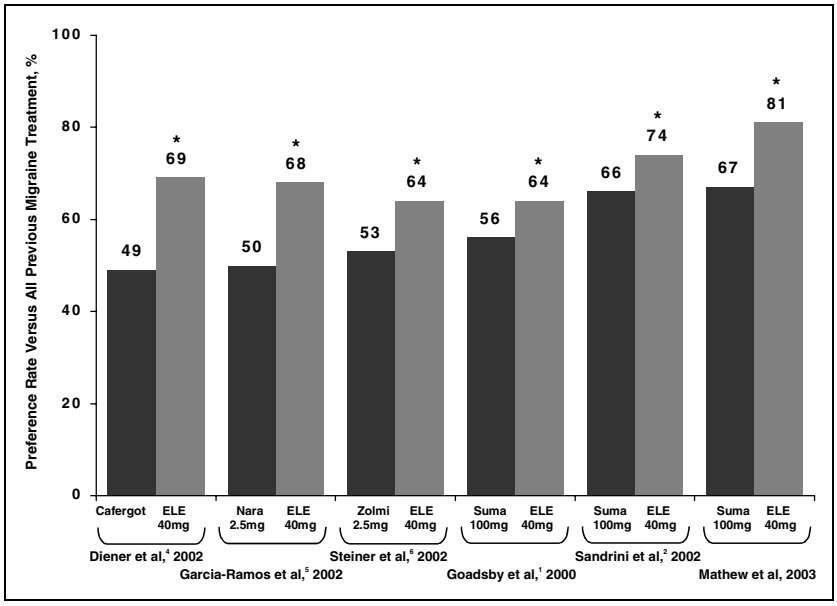

Fig 6.—Patient preference for current versus previous migraine treatment: results of 6 head-to-head eletriptan comparative trials. *$P < .05$ eletriptan (ELE) versus comparator. Nara indicates naratriptan; zolmi, zolmitriptan; suma, sumatriptan.

Figure 6 for the comparative trials whose efficacy results were previously summarized in Table 1. As can be seen, patient acceptability for migraine treatment is significantly higher for ELE-40 than for Cafergot or any of the 3 other triptans. When acceptability data is combined across the 4 studies that included both ELE-40 and ELE-80, mean preference ratings were 71% for ELE-40 and 73% for ELE-80 (Figure 6).

COMMENTS

Overall, eletriptan is well tolerated at the 3 doses studied in its clinical development program, ELE-20, ELE-40, and ELE-80 (Table 4). Eletriptan 20 mg has an excellent AE profile similar to placebo, with efficacy comparable to sumatriptan 100 mg.[1] Eletriptan 40 mg has individual AE rates only slightly higher than placebo, but with efficacy that is consistently superior to sumatriptan 100 mg. Eletriptan 40 mg is currently the highest recommended single dose in the United States because it appeared to have the optimal efficacy/tolerability profile for the majority of patients in extensive clinical trials. In head-to-head clinical trials, ELE-40 demonstrated significantly higher patient acceptability ratings (Figure 6) compared to other migraine-specific treatments (sumatriptan, naratriptan, zolmitriptan, and Cafergot). Finally, patients needing higher efficacy may benefit from ELE-80 (Table 1), where this is recommended.

Eletriptan is metabolized primarily by the CYP3A4 enzyme. Because of its high margin of safety, use of eletriptan is not recommended within at least 72 hours of treatment with a limited list of 7 potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir. This is because of the modest increase in AEs observed across a 4-fold dose increase from ELE-20 to ELE-80 (Table 4). Coadministration of CYP3A4 inhibitors examined across a range of inhibitory potency during a large long-term treatment study was not found to be associated with any clinically meaningful change in eletriptan tolerability (Figure 2). Furthermore, eletriptan neither induces nor inhibits any CYP enzyme, and so is unlikely to cause interactions with other drugs that might lead to changes in tolerability.

While concomitant use of eletriptan with the aforementioned potent CYP3A4 inhibitors is currently not recommended, it is nevertheless still important to establish the margin of safety for eletriptan at higher doses and plasma concentrations. To do so, eletriptan was administered intravenously in an angiography study to achieve a plasma concentration that was more than 2 times the C_{max} of ELE-40

when coadministered with a potent CYP3A4 inhibitor. At these higher eletriptan plasma levels, small dose-related decreases in coronary artery diameter were observed that were similar to those seen with a standard 6-mg SQ dose of sumatriptan (Figures 4 and 5).

Eletriptan is a substrate of the P-glycoprotein efflux pump (Pgp), which has been shown to modulate the transit of drugs into systemic circulation from the GI tract, and from systemic circulation across the blood-brain barrier into the central nervous system. The Pgp and CYP3A4 have extensive overlap in substrate specificity, but the clinical relevance of Pgp inhibition appears to be very limited since drugs that have Pgp inhibitory effects only cause inhibition at plasma concentrations that are above the levels achieved during therapeutic dosing.[23]

Across other parameters, eletriptan has a safety profile that is not notably different from other marketed triptans; it appears to have no effect on QTc or other ECG parameters, and is associated with no specific laboratory abnormalities. Eletriptan shares the class effect on BP, being associated with small and transient BP increases, primarily when a single dose of ELE-80 is administered. This effect was more pronounced in patients who were elderly or were renally impaired. Eletriptan is contraindicated in patients with uncontrolled hypertension.

Eletriptan: Efficacy/Tolerability Ratio.—This comprehensive review places the tolerability and safety of eletriptan in the broader context of the efficacy of the drug compared to other migraine-specific therapies based on head-to-head trials. The results indicate that the 40-mg dose of eletriptan offers superior efficacy to other marketed migraine therapies against which it has been tested (Table 1, Figure 4), and has a favorable tolerability profile that is associated with higher patient acceptability rates that are significant for ELE-40 versus comparative drugs (Figure 6).

Eletriptan 40 mg has significantly superior efficacy (Table 1) compared to sumatriptan 100 mg in 2 trials, in 1 trial each with Cafergot and naratriptan, and has numerical superiority compared to zolmitriptan. Such an efficacy advantage for one drug has not been consistently demonstrated for individual drugs in many other major classes of compounds such as the SSRI antidepressants, the COX-2 inhibitors, or the benzodiazepines. The efficacy advantage of eletriptan is not limited to the primary outcome—headache response at 2 hours. The publications and presentations reporting the results of the 6 head-to-head comparative trials[1-3,5-7] demonstrate that single doses of ELE-40 and ELE-80 also achieve significantly greater efficacy across most other secondary measures such as associated symptoms and functional response (Table 1).

In conclusion, review of an extensive safety database that includes more than 11 000 subjects demonstrates that eletriptan is a safe and well-tolerated addition to the armamentarium of acute treatments for migraine. Eletriptan has a tolerability and safety profile that is similar to other marketed triptans. Head-to-head comparative studies suggest that eletriptan has significantly superior efficacy at both the 40-mg and at the 80-mg doses. Patient acceptability ratings are consistently higher than for sumatriptan, naratriptan, zolmitriptan, and Cafergot because of the favorable efficacy/tolerability ratio of eletriptan.

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