

CLINICAL STUDY

Real-life experiences in migraine therapy

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Abstract: *Objective:* To evaluate the effectiveness of eletriptan for acute migraine treatment and patient satisfaction with the drug in usual clinical practice settings.

Methods: Male and female patients of practicing neurologists, aged 18 to 65 years, were eligible for inclusion in the study if they met International Headache Society criteria for migraine.

Results: Of 637 patients enrolled, 611 completed the study. At 1 hour post-dose headache response was 59.5 % (average from three attacks), pain-free 13 %, absence of vomiting 86.3 %, and improvement in functioning 55 %. Headache recurrence occurred in 12 %, second dose was used by 12.6 % patients, and rescue medication by 6.4 %. Patient preference for eletriptan versus any other triptan used in the past was 97 %.

Conclusion: In this real-life setting, eletriptan displayed high efficacy, consistency of response over three attacks and was preferred by 97 % patients (Tab. 2, Fig. 5, Ref. 16). Full Text (Free, PDF) www.bmj.sk.

Key words: migraine, usual clinic practice, eletriptan, patient preference.

The advent of selective agonists for serotonin 5HT_{1B/1D} receptors, a class of drug known as triptans, has substantially improved options for acute migraine therapy in the past two decades. Triptans specifically target several mechanisms that have been linked to migraine pathogenesis, including vasoconstriction of dilated extra cerebral intracranial blood vessels, reduction in neuropeptide release and plasma protein extravasation across dural vessels, and inhibition of nociceptive impulse transmission within the central nervous system (1). The efficacy and safety of triptans has been well established after 20 years of clinical experiences and numerous well-designed randomized clinical trials (RCT) (2, 3). Despite these facts, migraine is still suboptimally managed (4). Several population surveys showed that only about 30 % of patients are completely satisfied with their actual migraine therapy (5, 6, 7).

Currently, seven triptans with various pharmacologic properties are on market in Slovak Republic and with so many options available, it is difficult to decide which treatment is best for the specific patient. All oral triptans have comparable efficacy and tolerability; the direct comparison of triptans in controlled head-to-head trials is limited and so exact rules for triptan selection are missing (8). Physicians therefore need supportive evidence to make a rational choice between triptans. Valuable information

for differentiating among triptans is patient preference which reflects how given treatment is perceived by each patient (9).

The purpose of this trial was to provide guidance to physicians regarding patient preference using eletriptan, which due to its pharmacokinetic profile offers a high likelihood of treatment success (10). We used an open-label design that allows collection of data on eletriptan performance in real clinical practice.

Subjects and methods

Patients. Male and female patients, aged 18 to 65 years, were eligible for inclusion in the study if they met International Headache Society criteria for migraine with or without aura (11), reported at least one attack per 6 weeks over last 3 months, and at least one attack in the past was treated by any triptan. Patients were excluded for the following reasons: hypersensitivity to eletriptan or any of its inactive ingredients, severe renal or hepatic impairment, uncontrolled hypertension, ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or symptoms or findings consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or any other significant underlying cardiovascular disease, clinically significant arrhythmia or heart insufficiency, peripheral vascular disease, any history of cerebrovascular accident or transient ischemic attack, concomitant treatment with any other 5HT_{1B/1D} receptor agonist, ergotamine-containing or ergot-type medication.

The study was conducted at 48 neurological practices in the Slovak Republic in accordance with the Declaration of Helsinki, after approval by the local ethics committees. All patients provided written informed consent before entering the study.

Study design. This was an open-label, non-comparative, multicentre outpatient study in which patients treated 3 migraine

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Tab. 1. Patient demographics and baseline characteristics.

Sex/female (%)	86.2		
Mean age (years)	40.3±9.9		
Migraine diagnosis and history			
without aura (%)	61.4		
with aura (%)	38.6		
Duration since first diagnosis (years)	7.9		
Frequency over 6 week period	3.0±1.8		
Characteristics of treated attacks	1. attack	2. attack	3. attack
Headache rated moderate/severe (%)	86.5	94.8	93.4
Nausea (%)	78.0	86.4	84.0
Vomiting (%)	42.4	40.1	40.1
Photophobia (%)	69.5	72.6	70.7
Phonophobia (%)	69.5	72.6	70.7
Functional impairment rated moderate/severe (%)	80.5	85.4	84.6

attacks with eletriptan 40 mg or 80 mg (dose used was at patient's discretion). Patients were instructed to take study medication as soon as possible and within six hours after the onset of migraine headache provided that all of the following criteria are met: (i) the headache is judged by the patient to be a migraine attack and of an intensity that the subject normally would treat with a triptan; (ii) the headache's aura phase has ended; (iii) no analgesic or anti-emetic has been taken during the attack or during the preceding 6 hours; (iv) there have been at least 48 hours of freedom from headache since the last attack of migraine or, in case of recurrence, there has been a headache response and at least 2 hours have elapsed since the initial dose. Rescue medication was permitted if at least 2 hours elapsed since the second dose.

At the time of screening visit, patients were instructed in the completion of migraine diary. Patients were instructed to rate the intensity of their headache pain (severe pain, moderate pain, mild pain, no pain) and their degree of functional impairment (severe – requiring bed rest, moderate – working, studying, or housekeeping activities severely impaired/unable to perform but not requiring bed rest, mild – working, studying, or housekeeping activities reduced, absent – able to work and function normally in all activities despite the persisting headache or other symptoms).

The efficacy parameters consisted of the following: (i) headache response, defined as improvement in headache intensity to mild or no pain from a pretreatment level of moderate or severe; (ii) pain-free rate, defined as absence of pain; (iii) presence or absence of the associated symptoms of nausea, vomiting, photophobia, and phonophobia; (iv) change from pretreatment baseline on functional impairment scale; (v) headache recurrence, defined as the return of moderate to severe headache (from a previously improved level of mild or no headache) between 2 hours and 24 hours after ingestion of eletriptan; (vi) use of second dose of eletriptan; (vii) use of rescue medication; (viii) patient preference, rated on two point scale (prefer eletriptan, prefer previous treatment). Efficacy parameters were assessed at baseline (immediately before the treatment) and at 1, 2, and 24 hours after the dose.

Descriptive statistics were primarily employed to list and summarize the efficacy and safety outcomes as well as baseline characteristics of the patient sample. No inferential statistics were necessary because this was an open-label study without a control group.

Results

Baseline characteristics of patients. Six hundred and thirty-seven patients were screened, of whom 637 were assigned to the study treatment. Of them, 611 (96.2 %) completed the study, 13 patients (2.0 %) discontinued and 11 patients (1.7 %) were ongoing at date of cut-off. All patients were included in the safety population, 599 subjects were included in the intention-to-treat (ITT) population, and 570 in the per-protocol population. The

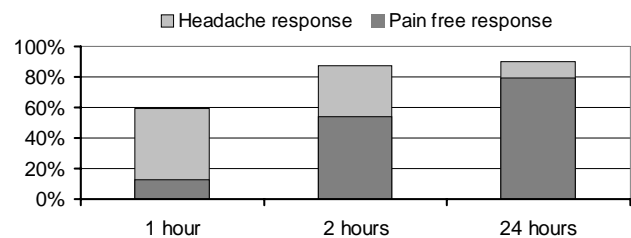


Fig. 1. Headache response and pain-free response rates on eletriptan regardless of dose in intention-to-treat population at 1 hour, 2 hours and 24 hours after dose (mean value from three attacks).

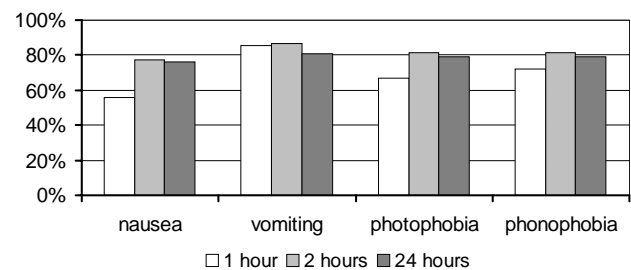


Fig. 2. Absence of associated symptoms on eletriptan regardless of dose in intention-to-treat population at 1 hour, 2 hours and 24 hours after dose (mean value from three attacks).

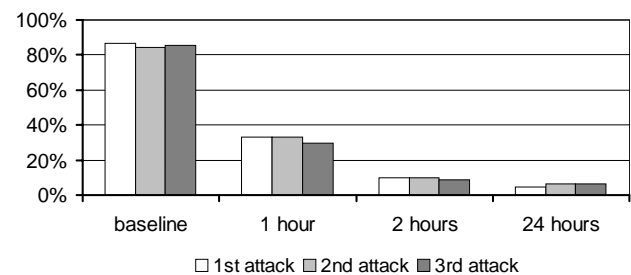


Fig. 3. Proportion of patients in intention-to-treat population with moderate to severe functional impairment at baseline and at 1 hour, 2 hours and 24 hours after dose.

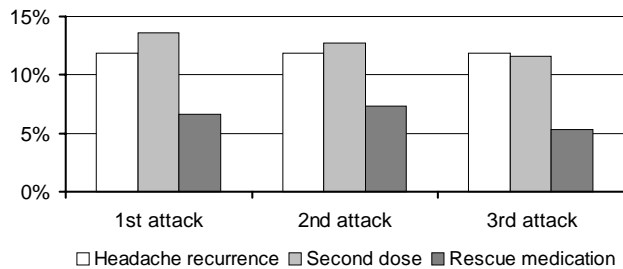


Fig. 4. Proportions of patients in intention-to-treat population regardless of eletriptan dose used with headache recurrence and those who took second dose and/or rescue medication.

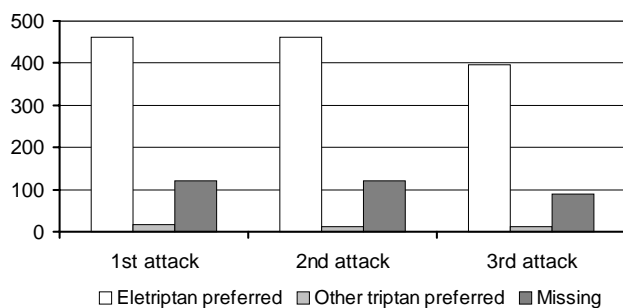


Fig. 5. Patient preference for eletriptan in intention-to-treat population.

typical study patient was a middle-aged woman with a long history of moderate-to-severe migraine headaches that usually occurred about once every 14 days and had one or more associated symptoms such as nausea, vomiting, photophobia, and phonophobia, as well as a high degree of functional impairment (Tab. 1).

Headache response and pain-free response. For the first attack of headache, the rate of response to the 40-mg dose of eletriptan at 1 hour after treatment was 57.7 %, at 2 hours 87.3 % and at 24 hours after the dose it was 91.5 %. Pain-free response rates were 11.9 % at 1 hour, 50.6 % at 2 hours and 80.0 % at 24 hours after the dose. 19 patients used eletriptan in a dose of 80 mg for the first attack and the headache response/pain-free response rates were similar, i.e. at 1 hour 57.9/53.3 %, at 2 hours 78.9/52.6 % and at 24 hours 84.2/73.7 %. Headache response rates and pain-free rates on both eletriptan doses were consistent across all three consecutive attacks without any marked differences. Pooled data from three attacks regardless of eletriptan dose for ITT population are summarized in Figure 1.

Absence of associated symptoms and improvement in functional impairment. Nausea was reported at baseline in 82.8 % patients (mean from three attacks in ITT population), vomiting in 40.9 %, photophobia in 70.9 %, and phonophobia in 83.5 % (Tab. 1). For the first attack treated with eletriptan in dose of 40 mg, the proportion of patients achieving relief at 1 hour was 53.4 % for nausea, 86.0 % for vomiting, 66.8 % for photophobia, and 71.1 % for phonophobia. The response rates were consistent across all three consecutive attacks regardless of eletriptan dose.

Pooled data from three attacks regardless of eletriptan dose for ITT population are summarized in Figure 2.

At baseline, 85.5 % to 87 % of patients reported moderate to severe functional impairment. Administration of eletriptan in dose of 40 mg resulted in marked and fast relief of functional impairment – at 1 hour after the dose, the proportion of patients reporting moderate to severe functional impairment was 32 % and after 2 hours only 9.1 % (Fig. 3). The effect was dose-independent since similar proportions were observed also in patients treated with eletriptan in dose of 80 mg.

Headache recurrence, use of second dose and use of rescue medication. Of patients with headache response within 2 hours, headache recurrence was reported by 12 % patients treated with eletriptan in dose of 40 mg. A similar rate was observed also in patients treated with eletriptan in dose of 80 mg and pooled data for three consecutive attacks are shown in Figure 4.

The patients were allowed to take the second dose of the study drug either due to non-response to the initial dose or for the treatment of headache recurrence. In the first attack, 6.9 % of patients treated with eletriptan in dose of 40 mg took a second dose. Proportions of patients who took a second dose were similar regardless of eletriptan dose used and were consistent across all three consecutive attacks. Pooled data regardless of eletriptan dose for ITT population are summarized in Figure 4.

Rescue medication could be used 2 hours after the second dose of eletriptan taken for non-response or for headache recurrence. For the first attack, rescue medication was required by 6.9 % of patients on eletriptan 40 mg and similar data were obtained also in patients treated with eletriptan 80 mg. Pooled data regardless of eletriptan dose are presented in Figure 4.

Patient preference. Of 479 patients who provided preference data for the first attack, 464 (96.9 %) preferred eletriptan to all previous triptans they had used for acute migraine treatment. The preference rate was consistent across all three consecutive migraine attacks (Fig. 5).

Tab. 2. Incidence and severity of treatment-emergent adverse events.

Body system	Eletriptan (n=637)				
	n	%	Severity		
Mild			Moderate	Severe	
Autonomic nervous					
Mouth dry	1	0.2	+	-	-
Cardiovascular					
Chest pain	1	0.2	-	+	-
Central and peripheral nervous					
Dizziness	1	0.2	+	-	-
Muscular hypertonia	1	0.2	+	-	-
Paresthesia	2	0.3	+	+	-
General					
Fatigue	1	0.2	+	-	-
Event inevaluable	1	0.2	-	+	-
Psychiatric					
Abnormal thinking	2	0.3	+	-	-

Safety and tolerability. The overall incidence of treatment-emergent adverse event was 1.6 %. All adverse events were described as mild or moderate and transient in nature. A complete list of adverse events is presented in Table 2. There were no serious adverse events reported. Over the course of the study, 13 (2.0 %) patients withdrew from the trial at some point after treating the first migraine attack. Three withdrawals (0.5 %) were considered as unrelated to study medication and were due to the patient treating fewer than 3 migraine attacks during the 3-month study period. The remaining patients withdrew because of lack of efficacy. No withdrawals were due to adverse event.

Discussion

In this real-life analysis of migraineurs across Slovak Republic we found that 97 % of patients preferred eletriptan to all other triptans they had previously used for acute migraine treatment. The presented data were obtained from a population in which 86 % to 93 % of patients reported suffering moderate to severe migraine attacks and more than 80 % of patients moderate to severe functional impairment. Despite this difficult-to-treat population, eletriptan was highly effective across the key clinical dimensions of migraine, including headache response, pain-free response, relief of associated symptoms, and improvement in functioning.

The efficacy data in this open-label study are consistent with previous placebo-controlled RCT of eletriptan (12, 13, 14) and provide additional confirmation of the efficacy of the 40-mg and 80-mg doses in treating the full range of migraine-related symptoms. Eletriptan was acting fast, at 1 hour after the dose, about 60 % patients had headache response and 13 % patients were pain-free. Similarly fast and effective were both eletriptan doses with regard to the relief of associated symptoms (at 1 hour after the dose, 55 %–70 % of patients were symptom-free) and of functional impairment (at 1 hour, 20 % of patients reported no functional impairment and severe to moderate impairment was present in only 32 % of patients). The obtained efficacy data are slightly higher than those reported in previous placebo-controlled RCT with eletriptan. We have no other explanation than the fact that our population consisted of experienced triptan users and that the response rate could be influenced by the open-label design.

An interesting observation was that there was no notable difference in efficacy between the 40-mg and 80-mg doses. This is in contrast to several previous reports where efficacy was apparently dose-dependent (12, 15). The reasons for the lack of clear dose-dependent effect in the present study are uncertain, but may be related to the fact that actual dose was decided by the patient who already had experience with triptan treatment and was aware of the severity of his attacks.

The most striking finding in our study was a relatively high, patient preference for eletriptan (more than 96 %) versus all other triptans they had used in the past. Patient preference is a patient-focused, composite outcome that incorporates efficacy, onset of action, duration of efficacy, consistency across attacks, tolerability and convenience of formulation [16]. Although patient pref-

erence is a subjective measure, it addresses the core issue as to which therapy is best for an individual patient, and reflects how particular treatment option is perceived by each patient with migraine (9). Based on this definition and taking in account overall performance of eletriptan in our study, the observed high preference for eletriptan is fully understandable. It reflects most likely the high and sustained pain relief, fast return to normal function, and absence of side effects. General validity of this observation has, however, several important limitations. Most notably, the study was not randomized and had no placebo control. Open-label study may be affected by patients' view about the study medication. The fact that eletriptan was given as a new treatment may also affect the perception relative to previous therapies. Our results might also have been biased by recall bias, since patient ratings of their previous migraine treatment were retrospective. Data based on retrospective recall tend to be less reliable than those collected prospectively.

Conclusions

The results of this open-label study reflective of real-life clinical practice, provide further evidence for the efficacy, consistency of response, safety and tolerability of oral eletriptan in the acute treatment of migraine headache, associated symptoms as well as functional impairment. Rapid, sustained symptomatic improvement and tolerability translated into 97 % patient preference for eletriptan versus any triptan used in the past. Despite the well-known limitations of studies with naturalistic design the presented data support the position of eletriptan as a first-line drug for the treatment of acute migraine.

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