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No effect of eletriptan administration during the aura phase of migraine

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Migraine aura is a warning sign readily recognized by patients. From the onset of aura it takes 30–60 min before the headache phase starts. Administration of acute medication during aura should provide sufficient time to achieve therapeutic plasma levels, counteracting the headache. To test this hypothesis we evaluated the efficacy of eletriptan 80 mg taken during aura. Patients met International Headache Society diagnostic criteria for migraine with aura, with an attack frequency of at least one per month and with aura occurring in >50% of recent attacks. Of 123 patients randomized, 87 (71%) were treated with a double-blind, one attack, during the aura phase before headache, dose of either eletriptan 80 mg ($n = 43$; 74% female; mean age, 40 years), or placebo ($n = 44$; 82% female; mean age, 40 years). The primary outcome measure was the proportion of patients not developing moderate-to-severe headache within 6 h post-dose. There was no significant difference in the proportion of patients developing moderate-to-severe headache on eletriptan (61%) versus placebo (46%). Eletriptan was well tolerated and did not prolong the aura phase. Typical transient triptan adverse events were observed; most were mild-to-moderate in intensity. This study confirms the findings of two studies showing that triptans are ineffective but safe when given during the migraine aura phrase.

Introduction

Epidemiologic studies indicate that approximately 64–68% of individuals have migraine with no preceding aura, 13–18% experience an aura prior to every migraine, and 13–18% have some attacks with and some without aura (Russell *et al.*, 1995; Lipton *et al.*, 2002). Although the International Headache Society Classification defines migraine with aura as a specific subform of migraine, most trials have included both migraine with and without aura. This is permissible because clinical trial guidelines (Tfelt-Hansen *et al.*, 2000) have not yet recommended separate analyses of response rates in migraine based on the presence or absence of aura. However, as migraine with aura constitutes a minority of the patients in migraine trials and there is some evidence (Pietrobon and Striessnig, 2003) that its pathophysiology might differ from migraine without aura, there is clearly a need for studies focusing specifically on migraine with aura. Furthermore, the presence of an aura offers the possibility to treat an attack very early in the hope that the painful phase of the attack might be completely prevented.

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In a previous study in which sumatriptan was injected during the aura phase, 68% of patients developed moderate-to-severe headache on sumatriptan 6 mg vs. 75% on placebo (Bates *et al.*, 1994). Use of sumatriptan during the aura was thus ineffective but safe and well tolerated, and did not prolong the aura. In a small crossover trial of 16 patients, zolmitriptan 20 mg in tablet form was administered during the aura and was similarly ineffective (Dowson, 1996). This surprising lack of effect of sumatriptan and zolmitriptan might not be valid for all triptans.

Eletriptan is a new triptan with proven efficacy in migraine and it has a longer half-life than sumatriptan or zolmitriptan. In the present double-blind, parallel-group, comparison study, we tested the hypothesis that eletriptan 80 mg given during the aura prevents the painful phase of a migraine attack. Additionally, we tested whether eletriptan would prolong the aura, a possible event because all triptans are vasoconstrictors and regional cerebral blood flow is known to be reduced in migraine with aura (Olesen *et al.*, 1981, 1990; Friberg *et al.*, 1994; Woods *et al.*, 1994; Cutrer *et al.*, 1998; Sanchez *et al.*, 1999). Finally, if eletriptan also proved ineffective, this study would make it almost certain that lack of efficacy during aura is a characteristic of the triptan class and, hence, would call for further studies of the possible reasons for the inefficacy.

Methods

Patients

Male and female patients aged 18 years and older who met International Headache Society (IHS) criteria for migraine with aura (Headache Classification Committee of the International Headache Society, 1988) with an attack frequency of at least one migraine with aura every 4 weeks were included. Patients were required to experience aura in at least 50% of their migraine attacks, with moderate-to-severe headache pain typically occurring within 6 h of the onset of aura.

Exclusion criteria included: (i) women who were pregnant, breastfeeding, or who were at risk for pregnancy and not using a medically proven form of contraception; (ii) patients who reported frequent, non-migrainous headache (> 6 per month); (iii) patients with migraines not quite fulfilling IHS criteria (probable migraine) or had consistently failed to respond to medical therapy; (iv) patients with any clinically significant medical illness or laboratory abnormalities, especially those indicative of coronary artery disease, heart failure, significant arrhythmias, or uncontrolled hypertension; (v) other contraindications to treatment with eletriptan including previous clinically significant allergic reaction to triptans; (vi) severe reduction in gastrointestinal absorption; and (vii) misuse of alcohol or other substances including analgesics, ergotamine, or triptans.

At screening, all patients had a physical examination, including blood pressure, 12-lead electrocardiogram (ECG), and urine pregnancy testing (as appropriate). Study conduct was consistent with the Declaration of Helsinki. The study protocol was 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 study entry.

Study design

This was a multicenter, double-blind, parallel-group, placebo-controlled evaluation of the safety and efficacy of eletriptan 80 mg when taken during the aura phase for the prevention of migraine headache. Patients were randomized to study treatment after they had first completed a practice session in which at least one acute migraine attack was treated with single-blind placebo in a manner consistent with the following study criteria: (i) the headache phase occurred within a 30-min to 6-h window after the onset of aura; and (ii) treatment was *not* taken if: (a) the patient had awakened with an aura; (b) the headache phase had begun at the time of dosing; (c) any analgesic or antiemetic medicine had been taken in the previous 6 h; (d) any triptan or ergotamine-like medicine had been taken in the previous 48 h; or (e) the patient were pregnant or had any recently emergent medical reason for not participating. During the practice attack, patients recorded details of the aura, the migraine headache, timing of treatment, and treatment response at 30 min, 1, 2, 6, and 24 h after taking the first dose of the study drug.

Patients reported to the clinic for re-evaluation within 2 weeks of practice attack treatment. Patients who had not successfully complied with all study procedures were permitted another practice attack. Based on practice attack information, patients were randomized to double-blind treatment if they met all of the following criteria: (i) had at least one attack of migraine in which the aura phase preceded the headache phase by 30 min to 6 h; (ii) had taken study medication (placebo) during the aura phase; and (iii) had satisfactorily completed the practice diary during the practice attack.

On the day of the prevention attack, patients self-dosed with two tablets of eletriptan 40 mg or matched placebo within 30 min of the onset of a typical aura provided they met the following criteria: (i) no migraine headache had started at the time of dosing; (ii) onset of aura was not during sleep (awoke with aura); (iii) no analgesic or antiemetic had been taken during the attack or in the previous 6 h; (iv) no other triptan or ergotamine-like agent had been taken in the previous 48 h; (v) the patient was not pregnant; and (vi) the patient was unaware of any acute change in their health status.

In the event that the patient developed a moderate-to-severe headache post-aura phase, a 40-mg eletriptan tablet was provided, both to patients randomized to initial eletriptan 80 mg, and patients randomized to placebo. In addition, patients were also provided with eletriptan 40 mg to treat up to two migraine headaches that developed without any prior aura, or that developed within 30 min of the onset of aura.

Assessments

During the treated attack, the time to onset of a moderate-to-severe headache was recorded in the diary in response to the question: 'When did your headache become severe or moderate?' Time to headache development was calculated relative to the time of the first dose of study drug for the prevention attack. Headache development was considered to be absent if a headache assessment of absent or mild was recorded in the diary

at each time-point (30 min, 1, 2, 6, and 24 h) post-dose. The duration of aura was also calculated based on the time of onset and offset recorded concurrently in the diary.

Patients recorded all migraine-related symptoms in their diary at standard time-points [baseline (immediately pre-dose), and at 30 min, 1, 2, 6, and 24 h post-dose]. Severity of headache pain was assessed on a four-point scale. Headache response was only calculated in the event that a second dose of study medication was taken for moderate or greater headache pain. Other efficacy measures included: (i) the need to take a second dose of study drug (at least 2 h after the first dose) to treat the migraine headache; (ii) use of rescue medication (and time to use) if the headache did not respond to the second dose; (iii) treatment acceptability, evaluated at 24 h post-dose by response to the question: 'Given the choice between this and any other medication to treat a migraine attack, would you take this again?'

Patients were asked to report adverse events, regardless of their causal relationship to the study drug. Physical examination, laboratory tests, vital signs, and 12-lead ECG were repeated at a follow-up visit, which occurred 7–14 days after the day of study treatment.

Statistical analysis plan

The intent-to-treat (ITT) sample included all patients with baseline and any on-treatment assessment data. The primary efficacy parameter was the proportion of subjects not developing a migraine headache of moderate or severe intensity within 6 h of dosing with a double-blind study drug. The primary analysis was conducted using a categorical linear model based on the SAS procedure CATMOD (SAS Institute Inc., Cary, NC, USA), which included terms for treatment and baseline severity. In case of a statistically significant between-treatment difference at baseline, adjustments were made.

Secondary end-points included time to headache development, duration of aura symptoms, use of second dose, response to the second dose, use of rescue medication, treatment acceptability, and time to rescue medication. Secondary end-points were analyzed using a categorical linear model based on SAS CATMOD procedure, which includes terms such as treatment and baseline severity. All statistical tests of significance were performed at the 5% level of significance, and were two-sided.

Results

Of 186 patients who were initially screened, 123 (66%) were randomized to the study drug (Fig. 1). The majority of the 36 (29%) patients who were randomized but not treated (Fig. 1) did not take study medication during the aura phase within the required 18-week window post-screening. The remaining 87 (71%) patients were randomized, took study treatment during the aura phase as specified in the protocol, and were included in the ITT analysis of the primary efficacy end-point, resulting in the development of moderate-to-severe migraine headache within 6 h post-dose.

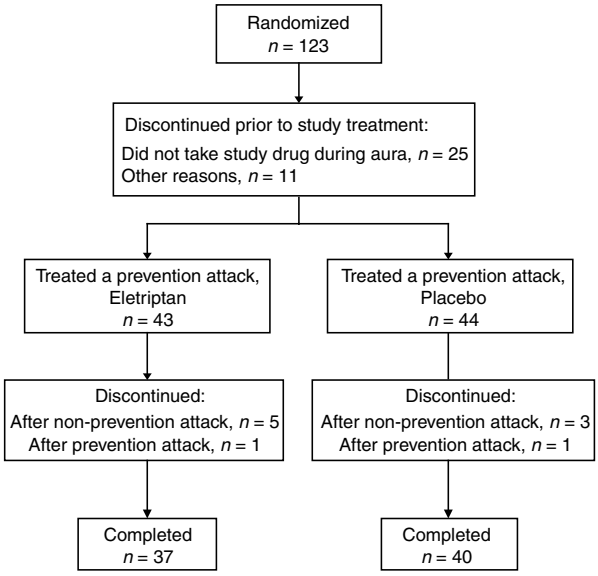

Figure 1 Patient disposition.

Baseline general clinical information on these patients is summarized in Table 1. Illness characteristics are typical of patients enrolled in triptan clinical trials, with the exception of the presence of aura. The majority of patients reported previous triptan treatment. The median duration of the aura during the practice attack was 0.8 h, almost identical to the duration of the aura during the prevention attack (Table 2).

Primary outcome: prevention of headache after treatment during aura

Treatment with eletriptan during the aura phase was not effective in preventing onset of moderate-to-severe headache post-aura (Table 2). There was a modest, but non-significant, higher proportion of patients developing a headache on eletriptan (61%) compared with placebo (46%).

Secondary outcomes

Eletriptan did not increase the duration of the aura phase compared with placebo (0.7 h vs. 0.8 h), nor was

Table 1 Clinical and demographic characteristics of the treatment sample

	Eletriptan 80 mg ($n = 43$)	Placebo ($n = 44$)
Female, %	74	82
Mean age, years (range)	40 (19–63)	40 (23–65)
Mean duration of illness, years (range)	21 (2–51)	23 (1–50)
Typical headache rated as moderate-to-severe, %	95	93
Monthly attack frequency of moderate-to-severe headaches[a] (mean)	2.8 per month	2.6 per month
Aura diagnosis		
With aura (%)	53	55
With and without aura (%)	47	45
Patients previously treated with sumatriptan, %	88	82

[a]Monthly average reported for 3 months prior to study entry.

Table 2 Efficacy measures after aura dosing[a]

	Eletriptan 80 mg ($n = 36$)	Placebo ($n = 41$)
Patients developing a moderate-to-severe headache within 6 h post-dose (%)	61	46
Median duration of aura	0.7 h	0.8 h
Median time to onset of headache	1.3 h	1.0 h
Use of second dose (eletriptan 40 mg) (%)	44	34
Response rate after second dose	54% (7/13)	53% (8/15)
Use of rescue medication (%)	28	17
Treatment was rated as acceptable at 24 h	76% (13/17)	72% (18/25)

[a]No significant differences between groups on any efficacy measure.

it associated with a significant delay in the median time to headache onset (1.3 h vs. 1.0 h).

A second dose of eletriptan 40 mg was permitted for patients in both the eletriptan and placebo treatment groups who developed a moderate-to-severe headache. Response rates to the 40-mg dose of eletriptan were similar in both (initial) treatment groups (Table 2). Additional rescue medication was taken by 28% of patients initially randomized to eletriptan 80 mg, and by 17% of patients initially randomized to placebo (Table 2). The percentage of patients rating study medication as acceptable was comparable for both eletriptan and placebo (76% vs. 72%; Table 2).

Tolerability and safety

Most adverse events were mild or moderate in severity and transient (Table 3). Of the all-causality adverse events reported on eletriptan, 30% were not considered to be treatment-related. One adverse event requiring description is that of a 38-year-old woman who took eletriptan 80 mg 10 min after the onset of aura. Ninety minutes later, during the headache phase, she experi-

Table 3 Treatment-emergent adverse events (all-causality incidence, %)

	Eletriptan 80 mg ($n = 37$)		Placebo ($n = 41$)	
	Used one dose ($n = 19$) (%)	Used two doses: Ele-80 → Ele-40 ($n = 18$) (%)	Used one dose ($n = 26$) (%)	Used two doses: PBO → Ele-40 ($n = 15$) (%)
Asthenia	21	0	0	7
Headache	11	0	8	7
Nausea	21	11	8	13
Vomiting	0	6	8	13
Dizziness	5	11	4	7
Hypertonia	5	0	0	20
Paresthesias	16	6	0	0
≥1 severe adverse event	14		10	
Discontinued due to adverse event	3		2	

enced moderate dizziness, confusion, and severe tiredness and muscle weakness. The episode, which was considered to be either atypical aura symptoms or possibly transient cerebral ischemia, resolved spontaneously at 6.8 h after onset. The patient was continued in the study. Subsequent computed tomography and magnetic resonance imaging evaluation of this patient did not reveal any abnormalities.

Post-treatment laboratory and ECG evaluations showed no clinically meaningful abnormalities.

Discussion

Efficacy

The results of the current study indicate that eletriptan does not prevent the development of headache pain if administered during the aura phase of migraine with aura. Eletriptan 40 mg used as rescue medication during the headache phase might have been effective, with a 2-h headache response rate of 53%, and a 2-h pain-free rate of 29%. The response in the present study might reflect a combined time and placebo effect. However, as both of the initial randomization groups were allowed to take eletriptan 40 mg as a rescue medication, there was no placebo control for this rescue dose. In a previous study, a rescue dose of injectable sumatriptan 6 mg, taken during the headache phase of migraine with aura did demonstrate significantly greater efficacy than a rescue dose of placebo (Bates *et al*., 1994).

Reasons for lack of triptan efficacy during aura

The lack of efficacy of sumatriptan, zolmitriptan, and eletriptan given during the aura raises interesting questions about the timing of treatment in relation to the underlying pathophysiology of migraine attacks. In the previously cited study (Bates *et al*., 1994) of subcutaneous sumatriptan versus placebo taken during the aura phase, the proportion of patients who developed a moderate or severe headache within 6 h after dose administration was similar in both groups (68% vs. 75%). Given its rapid absorption and onset of action, and its 2-h half-life, the lack of efficacy for subcutaneous sumatriptan taken during the aura phase cannot be due to inadequate plasma levels. In the present study an 80-mg oral dose of eletriptan was used. It might be questioned whether absorption was complete enough at the time of onset of headache pain. However, incomplete absorption and inadequate plasma levels appear to be an unlikely explanation because oral eletriptan has a T_{max} of 1.5 h, and even by 1 h the plasma level achieved by the 80-mg dose is higher than the T_{max} of the effective 40-mg dose of eletriptan. A small crossover study was also negative in which high-dose zolmitriptan (20 mg) versus placebo was taken during aura (Dowson, 1996). Similar to the current study, the high dose of zolmitriptan guarantees that plasma levels would have been achieved early and maintained long into the headache phase.

The results of the current study, taken together with those of the two previous studies, effectively exclude a pharmacokinetic explanation for the lack of efficacy of triptans during aura. A possible alternative explanation is that a blood–brain barrier impairment might be necessary for triptans to reach their site of action (Harper *et al*., 1977). It has been hypothesized that migraine attacks might be associated with such impairment. However, this possibility can be dismissed because the half-life of both eletriptan and zolmitriptan is at least 4 h, thus ensuring that plasma levels of each were high enough well into the time when the acute impairment in the blood–brain barrier has been hypothesized to occur.

It might be questioned whether the lack of efficacy of triptans taken during aura might be due to their ineffective nature in migraine with aura. The large numbers of patients used in the registration studies of triptans included mixed populations of migraine with and without aura. Furthermore, the diagnosis of the migraine aura was not usually standardized, and therefore might not have been very precise. Nonetheless, the evidence is conclusive from these trials that triptans work in both subtypes of migraine, even if their efficacy might be somewhat reduced in the aura subtype (Spencer *et al*., 1999). Only a single study focusing exclusively on migraine with aura has been negative for sumatriptan (Banerjee and Findley, 1992). In the present study, as well as the previous sumatriptan and zolmitriptan studies, patients who violated the protocol by not complying with the treatment until the headache phase had started had a positive treatment response to a triptan.

Discounting all the possible explanations discussed above, the possibility exists that early administration of a triptan, before the migraine attack has advanced sufficiently in its pathophysiologic cascade of events, actively blocks a later efficacy of triptans. One possibility is that acute tolerance might develop to triptan effects at the 5-$HT_{1B/1D}$ receptor. Further studies should examine this paradoxical self-inhibiting effect of the triptans. A complete understanding of these mechanisms might lead to new approaches to migraine treatment.

The pathophysiologic cascade leading to headache in migraine without aura is less well understood. Nonetheless, we hypothesize that pre-treatment with a

triptan, prior to the headache phase, would similarly fail to prevent onset of headache pain in migraine without aura. This is consistent with studies on cluster headache where no prophylactic effect of sumatriptan could be demonstrated (Monstad *et al.*, 1995).

Adverse events

Concern over the safety of administering vasoconstrictors such as triptans during the aura phase is related to extensive evidence(Olesen *et al.*, 1981, 1990; Friberg *et al.*, 1994; Woods *et al.*, 1994; Cutrer *et al.*, 1998; Sanchez *et al.*, 1999) indicating that aura symptoms are associated with a wave of oligemia that follows a transient hyperemia, and sweeps slowly across the occipital cortex at a rate of 2–6 mm per minute. Currently, evidence suggests that the oligemic changes associated with aura are not secondary to ischemia, and thus unlikely to be exacerbated or prolonged by administration of 5-$HT_{1B/1D}$ agonists. Instead, regional oxygenation appears to be adequate, with oligemia being secondary to reduced neuronal activity related to cortical spreading depression (CSD). CSD has long been hypothesized to be the substrate of the visual aura in migraine (Leao, 1944), and recent imaging studies have provided confirmation of this hypothesized link (Lauritzen and Olesen, 1984; Hadjikhani *et al.*, 2001).

Although CSD and aura are not primarily regional ischemic events, there is the epidemiologic link between migraine with aura and stroke, most notably in young women, and especially in those who smoke or use oral contraceptives (Tzourio *et al.*, 1995, 2000; Carolei *et al.*, 1996; Chang *et al.*, 1999). The nature of this correlation and its underlying mechanism remains to be elucidated, but it raises a concern that triptan use in this aura subgroup might be associated with an increase in stroke. A large prescription database study (Velentgas *et al.*, 2004) recently evaluated the risk of stroke amongst persons with migraine on triptan therapy versus those who were not. Current use of triptans was not associated with an increased relative risk [95% confidence interval (CI)] of stroke [0.90 (0.64–1.25)] or transient ischemic attack (TIA) [0.98 (0.66–1.45)]. Similarly, use of triptans was not associated with an increased relative risk of stroke [0.84 (0.46–1.55)] or TIA [0.99 (0.50–1.97)]. In the present study as well as in two previous studies, aura characteristics were prospectively recorded and eletriptan and other triptans did not aggravate or prolong the aura.

In conclusion, the results of the current study indicate that the administration of eletriptan during the aura phase of migraine is well tolerated but not significantly effective in preventing the development of migraine headache.

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