Brief Communication

Efficacy of Eletriptan in Migraineurs With Persistent Poor Response to Nonsteroidal Anti-inflammatory Drugs

Yook-Chin Chia, MBBS, MRCP; Shih-Hui Lim, MD; Shuu-Jiun Wang, MD;
Y. M. Cheong, MBBS, FRCPath; Jean Denaro, MA; Jayasena Hettiarachchi, MD

Background/Objective.—Nonsteroidal anti-inflammatory drugs continue to be one of the most widely used therapies for migraine, but their efficacy in treating moderate to severe migraine headache has not been well documented. In contrast, the efficacy of triptans in this group of patients is well documented, although no systematic research is available that evaluates the effectiveness of switching to a triptan in patients who respond poorly to nonsteroidal anti-inflammatory drugs.

Methods.—One hundred thirteen patients who met International Headache Society criteria for migraine and who did not experience satisfactory response to nonsteroidal anti-inflammatory drugs, received open-label treatment with a 40-mg dose of eletriptan for one migraine attack. Efficacy assessments were made at 1, 2, 4, and 24 hours postdose and consisted of headache and pain-free response rates, absence of associated symptoms, and functional response. Global ratings of treatment effectiveness and preference were obtained at 24 hours.

Results.—The pain-free response rate at 2 hours postdose was 25% and at 4 hours postdose, 55%; the headache response rate at 2 hours was 66% and at 4 hours, 87%. At 2 hours postdose, relief of baseline associated symptoms was achieved by 41% of patients with nausea compared to 82% of patients at 4 hours; for patients with phonophobia, 67% were relieved at 2 hours and 93% at 4 hours, and for patients with photophobia, 70% were relieved at 2 hours and 91% at 4 hours. Functional response was achieved by 70% of patients by 2 hours postdose. The high level of acute response was maintained over 24 hours, with only 24% of patients experiencing a headache recurrence and only 10% using rescue medication. At 24 hours postdose, 74% of patients rated eletriptan as preferable to any previous treatment for migraine. The most frequent reasons cited for this treatment preference were faster headache improvement (83%) and functional response (78%). Overall, eletriptan was well tolerated; most adverse events were transient and mild to moderate in severity. No serious adverse events were reported.

Conclusion.—Results of this open-label trial found the 40-mg dose of eletriptan to have a high degree of efficacy and tolerability among patients who responded poorly to nonsteroidal anti-inflammatory drugs.

Key words: eletriptan, nonsteroidal anti-inflammatory drugs, triptan, migraine, acute treatment, headache

Abbreviation: NSAIDs nonsteroidal anti-inflammatory drugs

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From University Malaya Medical Centre, Kuala Lumpur, Malaysia (Dr. Chia); Singapore General Hospital (Dr. Lim); The Neurological Institute, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan (Dr. Wang); Pfizer Pharmaceuticals Group, Kuala Lumpur, Malaysia (Dr. Cheong); and Pfizer Inc., New York, NY (Ms. Denaro and Dr. Hettiarachchi).

Address all correspondence to Dr. Jayasena Hettiarachchi, Pfizer Inc., 235 East 42nd Street, 10th Floor, New York, NY 10017.

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In the past decade, a series of randomized clinical trials have reported the efficacy of various nonsteroidal anti-inflammatory drugs (NSAIDs) for the acute treatment of migraine, typically in patients with less severe migraine than in patients in clinical trials with triptans.[1-12] A few comparative trials suggest that specific NSAIDs, such as diclofenac, may have faster onset than sumatriptan and ergotamine, and equivalent overall efficacy.[5,11,12] The efficacy of NSAIDs is frequently optimized by the addition of antiemetic drugs.[13]

Prescription survey data suggest that NSAIDs continue to be the single most widely prescribed class of medications for migraine (after aspirin), despite lack of Food and Drug Administration (FDA) approval for this indication, and despite a nonspecific mechanism of action that is not targeted at mechanisms hypothesized to be associated with migraine pathogenesis.[14] Some treatment guidelines suggest that all migraineurs initiate therapy with aspirin or an NSAID, only moving up to targeted treatment with a triptan in the event of treatment nonresponse.[15,16] This treatment strategy, which is called *step care*, has recently been shown to yield a less favorable outcome than "stratified care,"[17-19] which recommends immediate use of a triptan or other specific migraine therapies, such as dihydroergotamine, for any patient reporting a moderate or severe attack or associated impairment in functioning. Recent epidemiologic surveys suggest that at least 70% of migraineurs experience severe attacks or sufficient migraine-associated disability to qualify for immediate triptan treatment.[20] The proportion of migraineurs meeting stratified care criteria appears to be even higher among patients attending primary care practices.[21] Surveys conducted in primary care suggest that the majority of patients treated with aspirin or NSAIDs never "step up" to triptan therapy.[21] This results in patient dissatisfaction and poor compliance with medically supervised treatments.[22]

Despite recent data suggesting advantages for a treatment strategy based on stratified care, step care, utilizing over-the-counter drugs such as NSAIDs, continues to be the most widely used approach to migraine treatment. We are unaware of published research that examines the response to triptan therapy among patients who experience persistently poor response to initial NSAID treatment. The current study, using the 40-mg dose of eletriptan, was designed to obtain systematic clinical information on triptan response in this group who respond poorly to NSAIDs.

Eletriptan is a newer triptan with rapid and consistent absorption, high oral bioavailability, and potent agonist activity at 5-$HT_{1B/1D}$ receptors.[23-25] Eletriptan has demonstrated superior efficacy in head-to-head trials versus sumatriptan,[26-28] Cafergot,[29] zolmitriptan,[30] and naratriptan.[31] Eletriptan also has shown high response in patients who responded poorly to sumatriptan.[32] Recently, a double-blind, placebo-controlled study conducted in Asia confirmed the acute efficacy of eletriptan in migraine that had been previously demonstrated in Western studies.[33] There is no systematic research available in Asia, however, that evaluates the effectiveness of switching to a triptan in patients who responded poorly to NSAID therapy.

PATIENTS AND METHODS

Patients.—Men or women, aged 18 to 55 years, were eligible for the study if they met International Headache Society (IHS) criteria for migraine with or without aura,[34] reported between 1 and 6 acute migraine attacks every 6 weeks, and had a minimum illness duration of 1 year. Only those patients who responded poorly to treatment with NSAIDs were permitted to enter the study. To meet operational criteria for poor response, patients were required to meet all 3 of the following criteria: (1) treatment of at least 3 attacks with NSAIDs in the 3 months before study entry, (2) use of one or more of the following NSAIDs at the following minimum doses: naproxyn 500 mg, diclofenac 100 mg, ibuprofen 200 mg, ketoprofen 200 mg, tolfenamic acid 200 mg, or mefenamic acid 500 mg (the minimum doses represent the lowest doses for which efficacy has been demonstrated in previously published literature),[1-12] and (3) failure to respond adequately in at least 2 of the 3 consecutively treated attacks immediately before study entry. Failure to respond is defined by one or more of the following: continued severe functional impairment or need for bed rest 2 hours after treatment with an NSAID, or persistent moderate to severe head pain; intolerable associated symptoms (nausea, vomiting, photophobia, phonophobia); or a patient's expressed dissatisfaction with NSAID therapy due to either poor efficacy or poor tolerability.

Patients were excluded from the study if they reported: coronary artery disease, heart failure, uncontrolled hypertension or abnormal electrocardiogram (ECG); frequent nonmigrainous headache, treatment-resistant migraine, or migraine variants (eg, familial hemiplegic or basilar migraine); clinically significant allergic reaction to eletriptan or other 5-HT_1

agonists; use of potent CYP3A4 inhibitors in the 2 weeks before study entry; any clinically significant medical illness or laboratory abnormalities; severe reduction in gastrointestinal absorption; misuse or abuse of alcohol or other substances, including analgesics or ergotamine; use of any experimental drug within the previous month; and (for women) being pregnant, breast-feeding, or not currently using a medically accepted form of contraception.

The study was conducted at 13 centers in Asia (excluding Japan) according to the standards set forth in the Declaration of Helsinki (1996 revision) and consistent with all International Conference on Harmonisation Good Clinical Practice guidelines. An ethics review committee at each site approved the protocol. Study procedures were explained to prospective patients, and written informed consent was obtained before study entry. The screening medical evaluation consisted of a physical examination, vital signs, 12-lead ECG, and urine pregnancy testing (as appropriate).

Study Design.—This study was an open-label outpatient study in which patients treated one migraine attack with eletriptan 40 mg. Patients were instructed to take study medication when they experienced a typical migraine attack of moderate or severe intensity that was not improving. Patients took study treatment after the aura phase had ended, and within 6 hours of the onset of head pain. Treatment with study medication was not permitted if the patient had used an analgesic or antiemetic in the previous 6 hours, or had taken another triptan or ergotamine-containing or ergot-type medication (eg, dihydroergotamine) in the previous 48 hours. Patients were permitted to take a second dose of study medication for headache recurrence provided at least 2 hours had elapsed since the first dose. Rescue medication was permitted provided at least 2 hours had elapsed since the second dose of study medication.

Patients recorded migraine-related symptoms in a diary at baseline (immediately pre-dose), and at 1, 2, 4, and 24 hours postdose. Use of rescue medications also was recorded in the diary. Patients were not permitted to take any other triptan, ergotamine, or ergotaminelike substance for 24 hours postdose. Patients were asked to return to the study center for a final assessment within 14 days of the index attack.

Evaluation of Efficacy.—Efficacy parameters were assessed at baseline (immediately before treatment) and at 1, 2, 4, and 24 hours postdose. Efficacy parameters consisted of the following: (1) headache response, defined as improvement in headache intensity on a 4-point global intensity scale (0 = pain-free, 1 = mild, 2 = moderate, 3 = severe) to mild or pain-free levels from a pretreatment level of moderate or severe; (2) pain-free rates, defined as absence of pain on the 4-point scale; (3) presence or absence of associated symptoms of nausea, vomiting, photophobia, and phonophobia; (4) change from pretreatment baseline in a 4-point functional impairment scale (3 = bed rest, 2 = severe impairment in activities [work, study, housekeeping] but not requiring bed rest, 1 = some impairment in activities [work, study, housekeeping], 0 = normal level of functioning); (5) headache recurrence, defined as the return of a moderate to severe headache (from a previously improved level of mild or no headache) between 2 hours and 24 hours after ingestion of study medication; (6) use of rescue medication; (7) overall satisfaction with study medication, rated at 24 hours on a 7-point Likert scale ranging from 1 = completely satisfied to 7 = completely dissatisfied; and (8) acceptability of study medication, defined by the patient's answer to the following question: "Given the choice between this and any other previous medication you have used to treat a migraine attack, would you take this again?" Patients were asked to categorize the reasons for their preference into specific categories (eg, headache improvement was faster, improvement in associated symptoms was faster, return to normal activities was faster).

Statistical Analyses.—Descriptive statistics were provided on baseline characteristics and other end points. No inferential statistics were necessary because this was an open-label study without a control group.

RESULTS

Baseline Characteristics of Patients.—One hundred thirty-eight patients were screened, of whom 5 were disqualified. Of the 133 patients assigned to treatment, 20 never used the study medication, while 113 received at least one dose of study medication and constituted the intent-to-treat (ITT) sample. One patient was excluded from the efficacy analysis because she

Table 1.—Patient Demographics and Migraine Characteristics*

Feature	Eletriptan 40 mg Study Group (n = 113)
Female	81
Age, mean (SD), y	33.8 (9.2)
Range	18-54
Asian	100
Duration of illness, mean (SD), y†	7.9 (8.0)
Type of migraine	
Without aura	79.6
With aura	16.8
With and without aura	3.5
Frequency of attacks, mean (range), per month‡	3.2 (1-6)
Attacks rated as moderate to severe‡	84
Treated attack	
Severe	54
Nausea	74
Vomiting	24
Phonophobia	59
Photophobia	61
Moderate to severe functional impairment	86

*Values are percentage unless otherwise indicated.
†Time since first diagnosis.
‡Average over 3 months before study entry.

did not complete the diary (although she reported that she took 2 tablets of study medication on an unknown date), and one patient completed the study but was not included in the efficacy analysis due to invalid baseline headache assessment; all other patients completed the study. Demographic and clinical characteristics of the ITT sample are summarized in Table 1. Among this treatment sample with poor response to NSAIDs, the most common reported treatment was mefenamic acid (59%) followed by naproxyn (35%), ibuprofen (15%), and diclofenac (9%).

The most commonly cited reasons for poor NSAID response were persistent moderate to severe head pain at 2 hours (83%), global patient report of poor efficacy/tolerability (65%), and continued severe functional impairment and/or need for bed rest at 2 hours postdose (55%; patients were permitted to cite more than one reason).

Headache Response and Pain-free Response.— The headache response rate for the 40-mg dose of eletriptan at 1 hour postdose was 30%; 2 hours, 66%; and 4 hours, 87%. Pain-free rates were 8% at 1 hour, 25% at 2 hours, and 55% at 4 hours. Twenty-four percent of patients with headache experienced vomiting at baseline. Further evaluation of this subgroup revealed headache response in 27% at 1 hour, 67% at 2 hours, and 95% at 4 hours postdose.

Absence of Associated Symptoms and Improvement in Functional Response.—As summarized in Table 1, at baseline, nausea was reported in 74% of patients, phonophobia in 59%, and photophobia in 61%. Relief of these associated symptoms across the first 4 hours of treatment was achieved by 25% of patients with nausea at 1 hour postdose, 59% at 2 hours, and 82% at 4 hours; 43% of patients with phonophobia at 1 hour, 67% at 2 hours, and 93% at 4 hours; and in those patients with baseline photophobia, 36% reported relief at 1 hour postdose, 70% at 2 hours, and 91% at 4 hours. High rates of improvement in head pain and associated symptoms resulted in improvement in functioning, with functional response rates of 28% at 1 hour, 70% at 2 hours, and 81% at 4 hours. Complete symptom-free response, a stringent outcome measure consisting of the absence of all migraine symptoms of pain, associated symptoms, and functional impairment, was achieved at 4 hours by 52% of this group who responded poorly to NSAIDs.

Rescue Medication and Sustained Response.— Among patients who achieved a 2-hour headache response, 24% of these patients reported a recurrence and only 10% used any rescue medication. This resulted in a 52% sustained response rate (headache response at 2 hours with no subsequent recurrence and no use of rescue medication) at 24 hours.

Tolerability and Safety.—Treatment-emergent adverse events, reported regardless of relationship to study treatment (Table 2), were typically transient and mild to moderate in intensity. Somnolence (11.5%), nausea (9.7%), and vomiting (8.0%) were the most frequently reported adverse events. No patients discontinued the study due to adverse events, and no serious adverse events were reported.

Patient Global Assessment of Migraine Treatment.—Seventy-nine percent of patients were "satisfied" with eletriptan. Overall, 74% of patients preferred treatment with eletriptan to treatment with

Table 2.–Treatment-Emergent Adverse Events*

Adverse Event	Eletriptan 40 mg Study Group (n = 113)
Somnolence	11.5
Nausea	9.7
Vomiting	8.0
Asthenia	4.4
Dry mouth	3.5
Increased migraine pain	3.5
Chest symptoms	3.5

*Values are percentage. All causality with incidence ≥3%.

NSAIDs (and/or any previous migraine therapy). The top 2 reasons cited by patients for preferring eletriptan were faster headache response (83%) and faster return to normal functioning (78%).

COMMENTS

Few published studies systematically evaluate the efficacy of a triptan among nonresponders to previous NSAID treatment.[35] The results of this open-label trial found eletriptan 40 mg to be a highly effective acute treatment of migraine in patients who had reported consistently poor response to NSAID therapy. Headache response rates for eletriptan were high both at 2 hours (66%) and 4 hours (87%). Similarly, the majority of patients reported relief of phonophobia (67%) and photophobia (70%) at 2 hours, while 59% of patients achieved relief of nausea by 2 hours. Interestingly, the incidence of associated symptoms reported in the current study was notably higher than the rates reported in several of the previous controlled trials conducted in Asia.[33,34] This may reflect the selection bias introduced by limiting study entry to patients who reported poor response to NSAIDs.

Functional response showed a rate of improvement that paralleled improvement in head pain and associated symptoms, with 70% of patients achieving a functional response by 2 hours and 81% by 4 hours. The high level of acute response was maintained over 24 hours, with only 24% of patients experiencing headache recurrence and only 10% using rescue medication.

While the findings of this study provide useful clinical information, it should be cautioned that the results are preliminary and need further confirmation. The 2 major limitations of this study were the lack of randomized, double-blind design that included a placebo control, and the lack of prospective confirmation of NSAID nonresponder status. Previous studies have found that historical reports of nonresponse are confirmed by prospective treatment evaluation in approximately two thirds of cases.[36] We cannot be certain whether prospective treatment with NSAIDs would have led to the exclusion of up to one third of the study sample. The efficacy of eletriptan in the current study is unlikely to be primarily due to nonspecific factors such as placebo response. Research across multiple diagnoses, including migraine,[34] suggests that treatment-resistant patient samples have much lower placebo response rates than unselected samples.

Strength of open-label studies, such as the current one, is that they are more similar to actual clinical practice than phase III trials. As such, the results are more likely to be readily generalizable to clinical practice, guiding physicians in the choice of alternate and migraine-specific treatments for patients who have not achieved a satisfactory response to NSAIDs.

Overall, the 40-mg dose of eletriptan was well tolerated. The rate of treatment-emergent nausea (9.7%) and vomiting (8.0%) for eletriptan was relatively high in the current study compared to results from other studies. Previous trials, however, also have shown similarly high rates of nausea on placebo.[30,31] The lack of a placebo control group makes it impossible to evaluate the extent to which nausea and vomiting were symptoms of the acute migraine, as opposed to treatment-related adverse events. In addition, nausea, vomiting, and GI distress are the most frequent adverse events reported among patients treated with NSAIDs, with an incidence of more than 25% in some studies.[7] Gastrointestinal-related adverse events were almost as high on placebo in these same studies, indicating that an "expectancy effect" may have played a part. It is possible that a similar expectancy effect was present to drive up the rates of nausea and vomiting, but the lack of a placebo control group does not permit us to evaluate this hypothesis. The

incidence of somnolence was 11.5% in the current study, which was higher than the rate (5%) reported for the 40-mg dose of eletriptan in pooled data from almost 3000 patients treated in Western studies.[37] The reason for the higher rate of somnolence is uncertain, but may be due to recruitment of a biased sample, many of whom had reported dissatisfaction with NSAIDs due to poor tolerability. Alternatively, it may relate to ethnic differences in reporting adverse events.

The efficacy/tolerability profile of eletriptan was excellent, with the majority (79%) of patients expressing satisfaction with the 40-mg dose, and 74% stating a preference for eletriptan over all other migraine treatments they had used. The specific symptoms identified by patients at study entry that did not respond to treatment with NSAIDs appear to have been effectively treated by eletriptan, which demonstrated faster headache response (83%), improved functional response (78%), and complete relief of associated symptoms (64%).

In summary, the results of this open-label trial found the 40-mg dose of eletriptan to have a high degree of efficacy and good tolerability among patients who responded poorly to NSAIDs.

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