Early Migraine Intervention with Sumatriptan 100 mg in Patients with a History of Nonresponse to Sumatriptan 50 mg: An Open-Label, Prospective Study of Multiple Attacks

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ABSTRACT

Background: Early treatment with sumatriptan tablets (50 and 100 mg) has been shown to be effective in retrospective and prospective study designs. Despite the efficacy of sumatriptan 50 mg and early intervention, however, some patients continue not to respond completely to this dose. New evidence with a scientific basis for early intervention suggests that some patients may need to treat early to prevent the establishment of central sensitization. Also, patients cite complete pain relief as the most important attribute of a migraine medication.

Objective: The primary objective of this study was to determine the 2-hour efficacy of sumatriptan 100 mg in achieving complete pain relief in patients with a history of nonresponse to sumatriptan 50 mg in an early-intervention treatment paradigm. Secondary end points included complete pain relief at 4 hours, consistency of complete relief in at least 2 of 3 attacks, sustained complete relief over 24 hours, satisfaction with the 100-mg dose, and relief of associated symptoms.

Methods: This open-label, prospective study was conducted at the Wesley Headache Clinic (Memphis, Tennessee). Male and female patients between the ages of 18 and 65 years who fulfilled International Headache Society classification criteria for migraine, and who had a documented history of nonresponse to sumatriptan 50 mg at 2 hours after dosing when treating in the early, mild-pain phase in at least 2 of 3 migraine attacks were eligible for the study. Patients were instructed to receive one 100-mg sumatriptan tablet at the earliest sign of pain, while still mild, in 3 subsequent migraine attacks. After each treated attack, patients were to record a detailed diary entry.

Results: Twenty patients (17 women, 3 men; mean age, 44 years) treated all 3 migraines during the early, mild-pain phase and completed the study. Of the

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60 attacks treated, 48 (80%) were pain free at 2 hours, 56 (93%) were pain free at 4 hours, and 45 (75%) were pain free at 2 hours and continued to be pain free at 24 hours (sustained pain-free response). Sumatriptan 100 mg was well tolerated; none of the patients reported any adverse events.

Conclusions: In this study of migraineurs with a history of nonresponse to sumatriptan 50 mg at 2 hours after dosing in the early, mild-pain phase of migraine, increasing the dose of sumatriptan from 50 mg to 100 mg in the early-intervention paradigm, in most attacks complete pain relief was achieved for up to 24 hours. Because patients have indicated that becoming pain free was their therapeutic goal, based on the results of this study, physicians may want to consider increasing the dose of sumatriptan to 100 mg at the first sign of pain if the patient has consistently not responded to sumatriptan 50 mg in the early-intervention model. (*Curr Ther Res Clin Exp.* 2004;65:353–359) Copyright © 2004 Excerpta Medica, Inc.

Key words: early intervention, nonresponders, migraine, sumatriptan.

INTRODUCTION

Sumatriptan, a 5-HT_{1B/1D} agonist, has been shown to be effective in the treatment of migraine.¹ Post-hoc data analyses demonstrated that receiving sumatriptan while the pain is still mild optimizes pain-free efficacy.^{2–4} These findings were confirmed in 2 prospective, well-controlled trials.⁵ Burstein et al^{6,7} have provided both mechanistic and clinical data to further explain the biologic basis of the benefits of early intervention.

Freedom from pain is the most desirable goal of treatment for migraine, as evidenced when 87% of 688 patients rated this as their highest priority.⁸ The International Headache Society (IHS)⁹ recommends complete pain relief at 2 hours after dosing as the primary end point in its guidelines for controlled migraine trials.

Although both the 50- and 100-mg doses of sumatriptan are effective and well tolerated, more patients who have received both medications chose the 100-mg dose as optimal therapy.¹⁰ In a previous open-label study,¹¹ zolmitriptan 5 mg and rizatriptan 10 mg were effective in patients with a history of nonresponse to sumatriptan 50 mg. However, according to a MEDLINE search (key terms, *early intervention*, *nonresponders*, *migraine*, and *sumatriptan*; years, 1990–2004), there are no studies in which patients with a history of nonresponse to sumatriptan 50 mg are treated with sumatriptan 100 mg in an early-intervention paradigm.

The primary objective of this study was to determine the 2-hour efficacy of sumatriptan 100 mg in achieving complete pain relief in patients with a history of nonresponse to sumatriptan 50 mg in an early-intervention paradigm. Secondary end points included complete pain relief at 4 hours, consistency of complete relief in at least 2 of 3 attacks, sustained complete relief over 24 hours, satisfaction with the 100-mg dose, and relief of associated symptoms.

PATIENTS AND METHODS

Study Design

This open-label, prospective study was conducted at the Wesley Headache Clinic (Memphis, Tennessee). The institutional review board at Chesapeake Research Review, Inc. (Columbia, Maryland) approved the study protocol, informed consent, and diaries used in the study.

Patients

Male and female patients between the ages of 18 and 65 years who reported a 1-year history of IHS criteria for migraine with or without aura (1.1, 1.2)¹²; who had a documented history of nonresponse to 50-mg sumatriptan tablets at 2 hours after dosing in the early, mild-pain phase of at least 2 of 3 migraines; and who were able to understand the instructions for the study were eligible to participate. Patients were excluded if they had contraindications to triptans or any medical condition that would interfere with participation in a study. Patients were also excluded if they had headache >15 days per month within the 3 months before the study or participated in another investigative drug study within the 30 days before the study. Pregnant or breastfeeding women were excluded from the study. Women of childbearing age were required to use an effective method of birth control throughout the study.

Methods

Patients who met the eligibility criteria were instructed to receive one 100-mg sumatriptan tablet at the earliest sign of pain, while still mild, in 3 subsequent migraine attacks. Patients were allowed to receive 1 additional tablet (100 mg) or rescue medication 4 hours after the initial dose if they did not obtain complete pain relief.

At the screening visit, patients provided written informed consent, and a medical and migraine history and physical and neurologic examinations were completed. Patients also were instructed on how to complete a diary, and they completed the Headache Impact Test 6 (HIT-6).¹³ After each treated attack, patients were to record a detailed diary entry, including time to dosing, pain intensity, recurrence, use of rescue medications, and their level of satisfaction with the 100-mg dose using a 7-point Likert scale (1 = very dissatisfied, 2 = dissatisfied, 3 = somewhat dissatisfied, 4 = neutral, 5 = somewhat satisfied, 6 = satisfied, and 7 = very satisfied). Diaries were reviewed and summarized by clinic staff.

Patients returned to the clinic after treating 3 migraine headaches. The diary was reviewed with the patient to ensure accuracy and completeness. Adverse events (AEs) were recorded by the study coordinator (J.M.) in the patient chart.

The study investigators calculated the primary end point (ie, the percentage of migraine attacks in which complete pain relief was achieved at 2 hours after dosing). They also calculated the secondary end points, which included the

percentages of attacks with continued complete pain relief 4 hours after dosing and those with sustained complete pain relief (ie, complete relief at 2 hours and continued complete relief at 24 hours after dosing); and the percentages of patients with consistency of complete relief at 2 hours (ie, in 2 of 3 attacks), those who were satisfied with sumatriptan 100 mg, and those who had relief of associated symptoms (eg, nausea, vomiting, photosensitivity, phonosensitivity). Complete pain relief at 0.5, 1.0, and 1.5 hours after dosing also was assessed.

RESULTS

Study Population

A total of 20 patients (17 women, 3 men) were enrolled. Patients had a mean age of 44 years, a mean history of migraine of 23 years, and a mean age at onset of migraine attacks of 21 years. Seventeen patients (85%) had migraine without aura. The mean HIT-6 score was 64, indicating that migraine had a severe impact on their lives.

The most common migraine characteristics reported at the screening visit by patients were nausea (100%), photosensitivity (100%), phonosensitivity (90%), severe pain (85%), pain that worsens with activity (85%), pulsating pain (80%), and vomiting (75%). In addition to previous experience with sumatriptan 50 mg, the medications most commonly used previously were nonsteroidal anti-inflammatory drugs, zolmitriptan, and rizatriptan.

The most common pain characteristics at baseline directly prior to treatment were pulsating/throbbing pain (73%), unilateral pain (83%), tightening pain (52%), and neck pain/tightness (46%). The most common associated symptoms were photosensitivity (82%), phonosensitivity (73%), and nausea (42%). Other associated symptoms (nasal, optical, and sinus) were present but were not as common.

Treatment Outcomes

Fourteen of 20 patients (70%) dosed at the onset of their migraines, with a mean time to treatment of 7 minutes (range, 0–60 minutes); all patients received their medication for all attacks during the early, mild-pain phase.

In 48 and 56 attacks (80% and 93%, respectively) at 2 and 4 hours, complete pain relief was achieved. Eighty-five percent of patients were consistently pain free. In 45 attacks (75%), sustained complete pain relief was achieved over 24 hours (**Figure 1**). **Figure 2** shows an increase in the percentages of attacks in which complete pain relief was achieved over time.

Of the 60 attacks, only 3 attacks (5.0%) persisted, that is, headache intensity did not improve at 4 hours, necessitating the use of rescue medication; in 8 attacks (13.3%), patients experienced a return of migraine pain (recurrence) within 24 hours. Therefore, a total of 18.3% of attacks required rescue medication. Eight patients (40%) used rescue medication, 3 patients (15.0%) for 2 at-

Figure 1. Percentage of migraine attacks in which complete pain relief was achieved at 2, 4, and 24 hours after administration of sumatriptan 100 mg (N = 60 attacks).

Figure 2. Percentage of migraine attacks in which complete pain relief was achieved at 0.5, 1.0, 1.5, 2.0, and 4.0 hours after administration of sumatriptan 100 mg (N = 60 attacks).

tacks and 5 patients (25.0%) for 1 attack. Rescue medications included sumatriptan 100 mg for 9 attacks (15.0%); acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg for 1 attack (1.7%); and ibuprofen 400 mg for 1 attack (1.7%).

Two patients (10.0%) (1 attack each) medicated after 0.5 hour of pain. Both patients dosed at 1 hour and were pain free 2 hours after treatment.

Pulsating/throbbing pain, unilateral pain, and tightening pain were either not present or present in 4 of 60 attacks (7%) 4 hours after treatment. Similarly, photosensitivity or phonosensitivity were present in 5 attacks (8%), and nausea and/or vomiting in 3 attacks (5%) 4 hours after treatment.

Most patients (90%) were satisfied or very satisfied with sumatriptan 100 mg after having previously not responded to the lower dose (50 mg). None of the patients reported any AEs.

DISCUSSION

This study suggests that sumatriptan 100 mg may enable patients to become pain free by 2 hours and for up to 24 hours after dosing if they had not previously responded to sumatriptan 50 mg when treating in the early, mild-pain phase. These data support previous findings showing that most migraineurs who treat at the first sign of pain with sumatriptan 100 mg will achieve complete pain relief by 4 hours.⁵

These patients with a history of nonresponse to sumatriptan 50 mg reported a migraine history indicative of severe migraine (ie, a high HIT-6 score and incidence of nausea, vomiting, and other associated symptoms). The lack of AEs reported by the patients may be related to prior experience with sumatriptan 50 mg and increased tolerability of sumatriptan 100 mg in an early-intervention paradigm compared with patients treating moderate or severe migraine pain with sumatriptan 100 mg.⁵

The data from Burstein et al^{6,7} suggest that migraine pain may result from activation and sensitization of peripheral nociceptors, followed by central nociceptor sensitization. If patients treat their migraines at the earliest sign of pain, as in this study, this process may be interrupted, preventing the establishment of central sensitization, and allowing patients to become pain free.

CONCLUSIONS

In this study of migraineurs with a history of nonresponse to sumatriptan 50 mg at 2 hours after dosing in the early, mild-pain phase of migraine, increasing the dose of sumatriptan from 50 mg to 100 mg in the early-intervention paradigm, in most attacks complete pain relief was achieved for up to 24 hours. Because patients have indicated that becoming pain free was their therapeutic goal, based on the results of this study, physicians may want to consider increasing the dose of sumatriptan to 100 mg at the first sign of pain if the patient has consistently not responded to sumatriptan 50 mg in the early-intervention model.

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