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Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine

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Abstract

Objective—To reexamine the efficacy of terminating migraine headache by administration of sumatriptan during the visual-aura phase of the attack.

Background—Although the anti-migraine action of triptans is most effective soon after onset of the headache, treatment during the aura phase has been found to be ineffective.

Methods—Nineteen subjects having migraine with aura were studied using a four-way cross-over, open-label design. Each patient was asked to treat 8 consecutive attacks with 100 mg of sumatriptan RT: three attacks treated at a timing of the patient's discretion (baseline); one attack treated 4 h after onset of pain (late); two attacks treated within 1 h of onset of pain (early); two attacks treated during the aura phase – before the onset of pain (aura). Pain level and cutaneous allodynia were reported by the patients at the onset of pain, at the time of treatment, and 2 and 24 h after treatment.

Results—Sumatriptan treatment during the aura preempted the development of headache in 34/38 (89%) attacks. The same patients were rendered pain-free in 30/38 (79%) of attacks treated within 1 h of pain onset, and in 4/19 (21%) of attacks treated 4 h after the onset of pain. The incidence of allodynia at the time of treatment was 2/38 (5%) in attacks treated during aura, 8/38 (21%) in attacks treated early, and 14/19 (74%) in attacks treated late.

Conclusion—Considering the discrepancy between the present and previous clinical studies, it is worthwhile revisiting the efficacy of pre-emptive triptan therapy during the aura phase of migraine attacks, using larger-scale, three-way, cross-over, placebo-controlled studies.

Keywords

central sensitization; allodynia; headache; trigeminal; pain; nociception

INTRODUCTION

Administration of triptans during an early phase of a migraine attack, while the pain is still mild and the allodynia is not fully developed, increases the success rate of rendering the patient pain-free¹. Paradoxically, however, administration of triptan therapy during the aura phase of migraine has been shown to be ineffective in preventing the onset of headache or shorten its duration^{2–4}. These findings are particularly puzzling given that circulating levels of triptans

remain high for several hours after administration⁵, long enough to persist through the aura phase and into the subsequent headache phase. Since many patients still testify to the effectiveness of triptan treatment during the aura phase, we re-visited the timing of triptan treatment using a 4-way cross-over study design that compared the effects of 100 mg sumatriptan RT given during the aura phase *before* the onset of headache to the effects of same treatment given *after* the onset of pain. Given the novelty of the potential role central sensitization plays in triptan treatment and the need to test this concept in large double-blind placebo-controlled randomized studies using quantitative sensory testing, the current study was designed to generate an hypothesis in a proof-of-concept approach that limits the number of patients to the minimum needed.

METHODS

Patient Recruitment and Selection

The protocol was approved by the Western IRB and each patient provided written informed consent prior to participation in the study. Thirty-two patients exhibiting visual aura with every headache were recruited from the Headache Center. Patients were included in the study if they fulfilled the International Headache Society criteria for migraine with visual aura ICHD 1.2.1; used no more than one prophylactic medication; and were able to understand and comply with the protocol and data entry into an electronic diary. Patients were excluded from the study if they had migraine headache that were not preceded by aura, if they had frequent tension headaches; ill-defined head pain; had more than an average of 3 headache days a week or more than 15 headache days per month in the 3 months preceding the study; had migraine with motor aura; used opiates to treat migraine; or required daily use of centrally-acting medications. Also excluded were pregnant and lactating women and women not on adequate birth control.

Study Procedures

In the first phase of the study (baseline), each patient was required to document 3 consecutive migraine attacks in which visual aura preceded the onset of headache by 30–60 minutes. Patients were instructed to treat these attacks with 100 mg sumatriptan RT at a timing of their own discretion. Patients kept a detailed electronic diary which was updated and sent via the web and/or by paper copy. This method was done to ensure that all patients had migraine pain after aura 100% of the time and also to train patients to recognize symptoms of allodynia. Recorded data included time of aura onset, time of headache onset, headache location, allodynia symptoms, time of treatment relative to the onset of aura and onset of pain, positive and negative characteristics of visual aura, and pain level. Pain level and allodynia symptoms were documented at onset of pain, time of treatment, and 2 and 24 hours after treatment.

After documenting and treating 3 baseline attacks, patients were instructed to treat 5 subsequent attacks in the following order: treat attack 1 at 4 h after onset of headache (late phase); treat attacks 2 and 3 within 1 h of onset of pain (early phase); treat attacks 4 and 5 during the aura before the onset of pain (aura phase).

Allodynia questionnaire

Do you experience pain or unpleasant sensation *on your skin* during a migraine attack when you engage in *any* of the following activities (Yes, No, or Not Applicable): (1) combing your hair; (2) pulling your hair back (example: ponytail); (3) shaving your face; (4) wearing eyeglasses; (5) wearing contact lenses; (6) wearing earrings; (7) wearing necklaces; (8) wearing anything tight on your head or neck (hat, scarf); (9) wearing anything on your arm or wrist (bracelet, watch); (10) wearing a finger ring; (11) wearing tight clothes; (12) being covered with a heavy blanket; (13) taking a shower (when shower water hits your face); (14) resting your face on the pillow on the side of the headache; (15) being exposed to heat (examples:

cooking; placing heating pads on your face); (16) being exposed to cold (examples: breathing through your nose on a cold day; placing ice packs on your face).

Data Analysis

The primary endpoint was pain-free status 2 h after treatment. The secondary endpoint was sustained pain-free, defined as pain-free at 2 h sustained through 24 h. Data were analyzed using χ^2 test. Level of significance was set at 0.05.

RESULTS

Of the 32 patients recruited in the study, 13 failed to complete the study for the following reasons: one patient was intolerance to sumatriptan; seven did not experience aura in all 3 baseline attacks; three were lost to follow-up; two withdrew their consent. Nineteen patients (84% Caucasian) completed the study. Their mean age was 39.8 years, and had a migraine history averaging 21.3 years. The incidence of migraine symptoms in the baseline attacks recorded were as follows: throbbing – 84%; nausea – 95%; vomiting – 11%; photophobia – 100%; phonophobia – 100%; allodynia – 84%.

Baseline Attacks

Of 57 attacks treated at the discretion of the patients, 44 (77%) were treated within 1 h of onset of pain (36.9 ± 3.2 min; mean $\pm$ SEM). The remaining 13 attacks were treated between 90 and 240 min after onset of pain (147.7 ± 13.2 min). Pain-free status at 2 h after treatment was achieved in 66% of attacks treated <1 h from the onset of pain vs. 23% of the attacks treated >1 h ($\chi^2 = 7.48$, $df = 1$, $p = 0.006$).

Attacks Treated During Aura Phase vs. Headache Phase

Thirty-eight attacks were treated between 0 and 15 min from the onset of aura – in advance of the onset of pain. Thirty-eight attacks were treated between 0 and 1 h (34.4 ± 4.6 min) from the onset of pain. Nineteen attacks were treated 4 h after pain onset. Of 38 attacks treated during the aura phase, 34 (89%) did not develop the headache phase; in the same patients, the incidence of pain-free status within 2 h of treatment was 30/38 (79%) for attacks treated within 1 h of onset of headache, and 4/19 (21%) for attacks treated 4 h after the onset of headache. ($\chi^2 = 37.63$, $df = 2$, $p < 0.0001$).

Based on the questionnaire data, the incidence of allodynia at the time of treatment was 2/38 (5%) for attacks treated during aura, 8/38 (21%) for attacks treated early, and 14/19 (74%) for attacks treated late ($\chi^2 = 32.00$, $df = 2$, $p < 0.0001$). Regardless of time of treatment, pain-free status at 2 h post sumatriptan was achieved in 64/71 (90%) of attacks treated in the absence of allodynia vs. 4/24 (17%) of attacks treated in the presence of allodynia ($\chi^2 = 47.60$, $df = 1$, $p < 0.0001$).

The relationship between time of treatment, pain-free status at 2 h after treatment, and presence or absence of allodynia at time of treatment are illustrated in Fig. 1.

Sustained Pain-Free

Pain status at 24 h post-triptan was available for 34/38 attacks treated during aura. Headache did not develop in any of the 34 attacks within 2 h of treatment, and only in 2 cases (6%) headache was present 24 h later. Pain status at 24 h post-triptan was reported in 31/38 attacks treated within 1 h after onset of pain. Headache was terminated within 2 h of treatment in 29 attacks, and in 25 of those (86%) the pain-free status was sustained over 24 h.

Side Effects

Side-effects included drowsiness (10.5%), dizziness (8%), flushing (5%) and palpitations (2%). One patient dropped out because of developing chest-tightness.

DISCUSSION

Treating migraine with sumatriptan within the first 15 minutes of the aura phase proved extremely effective in preempting the onset of migraine headache. Our findings stand in contrast with previous studies, in which treatment with triptans was ineffective during the aura phase of migraine²⁻⁴. In view of this discrepancy, we would like to urge other groups to revisit the efficacy of triptans during the aura phase of migraine using larger-scale, three-way, cross-over, placebo-controlled studies.

The anti-migraine action of triptans appears to be mediated through 5HT_{1D} receptors on central terminals of meningeal nociceptors in the spinal trigeminal nucleus⁶. The ineffectiveness of triptans reported in the earlier studies has been attributed to temporal inaccessibility of central neurons to drug action. According to one hypothesis, the blood-brain barrier remains impermeable to triptans during the aura phase of migraine, and opens up only later during the headache phase⁷⁻⁹. According to a second hypothesis, 5-HT_{1D} receptors on the central terminals of nociceptors are stored in synaptic vesicles in the absence of pain, and are being incorporated in the synaptic membrane – thus available to binding – only after the onset of pain¹⁰. The preemption of migraine headache by sumatriptan reported in the present study suggests that the blood brain barrier is not completely shut off during aura, thus permitting sufficient levels of sumatriptan to reach the central site of action. The present findings also suggest that 5-HT_{1D} receptors are not completely absent from the membrane of the central terminals of meningeal nociceptors before the onset of headache, and that the numbers of receptors available for binding may be sufficient to permit the anti-migraine action of sumatriptan during the aura.

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Figure 1.

Anti-migraine effects of 100 mg sumatriptan RT as it related to the time of treatment and occurrence of cutaneous allodynia. Number of attacks is indicated above each bar (key for bar labeling as indicated in the figure). Notice that treatment during the aura phase of the attack was extremely effective in preempting the development of migraine headache. This success rate was comparable to the high efficacy of treatment given within 1 h of onset of headache.