Brief Communication

Naratriptan in the Preventive Treatment of Refractory Chronic Migraine: A Review of 27 Cases

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Objective.—To review the efficacy of naratriptan as preventive treatment in 27 patients with chronic migraine refractory to other commonly used preventive therapies.

Background.—The treatment of chronic migraine often poses a major challenge to the clinician. Even when given expert care, patients with chronic migraine may continue to have daily or near-daily headaches.

Methods.—Clinical records and headache calendars were reviewed of 27 patients fulfilling the following inclusion criteria: (1) aged 18 to 65 years; (2) diagnosis of chronic migraine (formerly transformed migraine), according to the criteria proposed by Silberstein et al; (3) previous failure of at least 4 preventive medications prescribed as part of a management program that included nonpharmacological measures, preventive medication, acute care medication, and detoxification from overused medication; and (4) have used daily naratriptan for no less than 2 consecutive months. The dose of naratriptan prescribed was 2.5 mg twice daily. We considered the following outcomes: (1) frequency of headache, (2) intensity of pain, (3) number of days per month with severe headache, (4) headache index (frequency times intensity), and (5) proportion of patients who reverted to an episodic pattern of pain after 6 months of treatment.

Results.—There was a statistically significant reduction in the frequency of headache days 2 months (15.3 days versus 24.1 days at baseline, $P<.001$), 6 months (9.1 days, $P<.001$), and 1 year (7.3 days, $P<.001$) after daily treatment with naratriptan was initiated. There was also a statistically significant reduction in the number of days per month of severe pain at 1 month (5.6 days versus 12.5 days at baseline, $P<.01$), 2 months (5.7 days, $P<.01$), 6 months (2.8 days, $P<.01$), and 1 year (2.6 days, $P<.01$). Similarly, there was a statistically significant reduction in the headache index at 2 months (33 versus 56.4 at baseline, $P<.001$), 6 months (19.5, $P<.001$), and 1 year (17.2, $P<.001$).

Of the 20 patients who continued to use naratriptan daily for at least 6 months, 13 (65%) reverted to an episodic pattern of pain (migraine). At 1 year, 11 (55%) still continued to experience episodic headache, 1 (5%) relapsed to chronic migraine, and 2 (10%) were lost to follow-up. No patients had intolerability to naratriptan during the treatment period, and no one stopped treatment due to adverse events.

Conclusion.—Naratriptan may have a role in the preventive treatment of intractable chronic migraine. Prospective, controlled studies should be considered.

Key words: chronic migraine, chronic daily headache, transformed migraine, naratriptan, preventive treatment, prophylactic treatment

Abbreviations: CDH chronic daily headache, CM chronic migraine

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Chronic daily headache (CDH), usually defined as headache which occurs more than 15 days a month (or 180 days a year) for more than 4 hours a day, is one of the more frequently seen headache syndromes at major tertiary care centers worldwide.[1-3] Its prevalence is almost 5% in the general population.[4-5] Chronic migraine (CM) is the most common form of CDH.[2,3,6,7] This disorder has been variously called *transformed migraine*, *evolutive migraine*, or *mixed headache syndrome.* Patients with CM usually have a past history of episodic migraine, reporting a process of transformation characterized by headaches that become more frequent over months to years, with the pain intensity and associated symptoms becoming less severe.[8] Such patients often develop a pattern of CDH that phenomenologically may resemble chronic tension-type headache with attacks of typical migraine superimposed.[1] They often have headaches 28 days or more per month.[9]

The treatment of CM often poses a major challenge to the clinician. It requires a multidisciplinary approach, employing behavioral medicine techniques, daily preventive and appropriate acute care medications, and partial or full withdrawal of any acute care medication that is being overused. To a great extent, treatment success depends upon the medications used, singly or in combination. Even with expert care, a significant percentage of these patients still persist with daily or near-daily headaches.[10-13]

The triptans represent a benchmark in the acute treatment of migraine. Their mechanism of action is based on the stimulation of specific serotonin (5-hydroxytryptamine [5-HT]) receptors, including peripheral $_{1B}$ and central and peripheral $_{1D}$ subtypes.[14] The oral triptans can be divided into two groups. Group 1 consists of those with faster onset and higher potency: sumatriptan, zolmitriptan, rizatriptan, almotriptan, and eletriptan. Group 2 consists of the slower-onset oral triptans with lower overall potency, lower rates of early headache recurrence, and a more favorable side effect profile: naratriptan and frovatriptan.[15-19]

Naratriptan was the third selective 5-HT$_{1B/1D}$ agonist to be introduced in the United States for the acute treatment of migraine. In a previous study by Sheftell et al, three patients with CM previously refractory to a wide variety of traditional preventive pharmacologic and nonpharmacologic interventions experienced a remarkable reduction in the frequency and intensity of daily headache while receiving preventive treatment with daily naratriptan.[20] Subjective improvement in quality of life and restoration of normal functioning (including a decrease in missed workdays) also was reported by those patients.

The aim of this study was to review retrospectively the efficacy of naratriptan in the preventive treatment of 27 patients with CM refractory to other standard preventive medications.

METHODS

This study was performed at The New England Center for Headache (NECH), Stamford, Conn. Clinical records and headache calendars (diaries) were reviewed of 27 patients fulfilling the following inclusion criteria: (1) aged 18 to 65 years; (2) diagnosis of CM (formerly transformed migraine) according to the criteria proposed by Silberstein et al[21] (Table 1); (3) previous failure of at least 4 preventive medications prescribed as part of a management program that included nonpharmacological measures and detoxification trials; (4) daily use of naratriptan for no less than 2 consecutive months; and (5) stable dose of medication used to prevent CM in the last 2 months.

The decision to use naratriptan in the patients presented was based on their refractoriness to other preventive therapies (alone and in combinations), as

Table 1.—Proposed Revision to International Headache Society (IHS) Criteria for Transformed Migraine[21]

A. History of episodic migraine meeting any IHS criteria 1.1 to 1.6
B. Daily or almost daily (>15 days/month) head pain for >1 month
C. Average headache duration of 4 hours/day (if untreated)
D. History of increasing headache frequency with decrease in severity of migrainous features over at least 3 months
E. At least one of the following:
   1. There is no suggestion of one of the disorders listed in groups 5-11
   2. Such disorder is suggested, but is ruled out by appropriate investigation
   3. Such disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder

well as on the good results obtained in three previous patients followed in the same headache center (not included in this study).[20] Patients were enrolled in this study no less than 6 months after they had tried and failed a headache management program. Patients were formally informed that daily dosing of a triptan was an "out-of-label" use, that this was an experimental treatment and certain risks would be undertaken, and were included after informed consent.

Once the patient decided to participate in the study, all preventive drugs were stabilized and naratriptan 2.5 mg twice daily was added. The medication was often begun at one half tablet in the morning and increased every 3 days by half a tablet until the final dose of one tablet twice per day was attained. Headache calendars were reviewed and the parameters of the month immediately previous to the naratriptan prescription were considered as the baseline. For extremely severe breakthrough headaches, occasional use of fast-onset triptans was permitted (after careful explanation that this was an off-label use, and increased the risk of cardiovascular adverse effects).

We considered the following outcomes: (1) frequency of pain; (2) intensity of pain, measured on a scale ranging from 0 (no pain) to 3 (severe pain); (3) number of days with severe headache per month; (4) headache index (frequency times intensity); and (5) proportion of patients that reverted to an episodic pattern of pain after 6 months of treatment. The outcomes from numbers 1 through 4 were compared to the baseline period after 1 month, 2 months, 6 months, and 1 year.

Descriptive statistics were applied. The assumption was that the values were sampled from Gaussian distributions and tested using the normality test of Kolmogorov-Smirnov. Matched comparisons in nonparametric distributions were performed using the Friedman test with posttest. Nonmatched comparisons in nonparametric distributions were performed using the Kruskal-Wallis test with posttest.

RESULTS

Our sample consisted of 27 patients, 20 (74.1%) of whom were women. Ages ranged from 18 to 64 years, with a mean age of 44.5 years (standard deviation [SD], 12.0; 95% confidence interval [CI], 42.8 to 52.3). All patients were followed for at least 1 year after being given naratriptan. The average length of treatment at The NECH, for these patients, was 5.3 years.

Prior to their first visit to the center, 24 patients (88.9%) had taken at least 1 preventive drug (Table 2). At The NECH, all patients were submitted to an optimized approach to CM that included nonpharmacological techniques, detoxification when the patient was overusing acute medications, and a regimen of preventive medication. The number of preventive drugs tried before inclusion in the naratriptan study ranged from 4 to 21 (average of 7.2). When included, 14 patients (51.8%) were using 1 preventive drug, 12 (44.4%) were using 2 preventive drugs, and 1 (3.7%) was using 3 different preventive drugs. At the moment of inclusion in the study, 13 patients (43.1%) were overusing acute care medications, despite the previous attempts at detoxification. Four (14.8%) were overusing butalbital compounds; 4 (14.8%), acetaminophen combined with acetylsalicylic acid (ASA) and caffeine; 2 (7.4%), opioids; 2 (7.4%), nonsteroidal anti-inflammatory drugs (NSAIDs); and 1 (3.7%), ASA.

Of the 27 patients who completed the evaluation at 2 months (criteria of inclusion), 20 (74.1%) continued to use naratriptan after 6 months and 18 (66.7%) after 1 year of inclusion. All the patients who stopped using naratriptan except 1 were acute medication overusers.

At inclusion, 13 (43.1%) of 27 were overusing acute care medications. At 6 months, 6 (30%) of 20; at 1 year, 5 (27.8%) of 18. These differences are not statistically significant.

Table 2.—Pharmacologic Classes of Preventive Drugs Used by Patients Prior to Admission to Headache Center

Pharmacologic Class	No. (%) of Patients
Beta-blockers	21 (77.8)
Tricyclic antidepressants	15 (55.6)
Selective serotonin reuptake inhibitors	10 (27.3)
Anticonvulsants	10 (27.3)
Calcium-blockers	6 (22.2)
Serotonin agonists	2 (7.4)

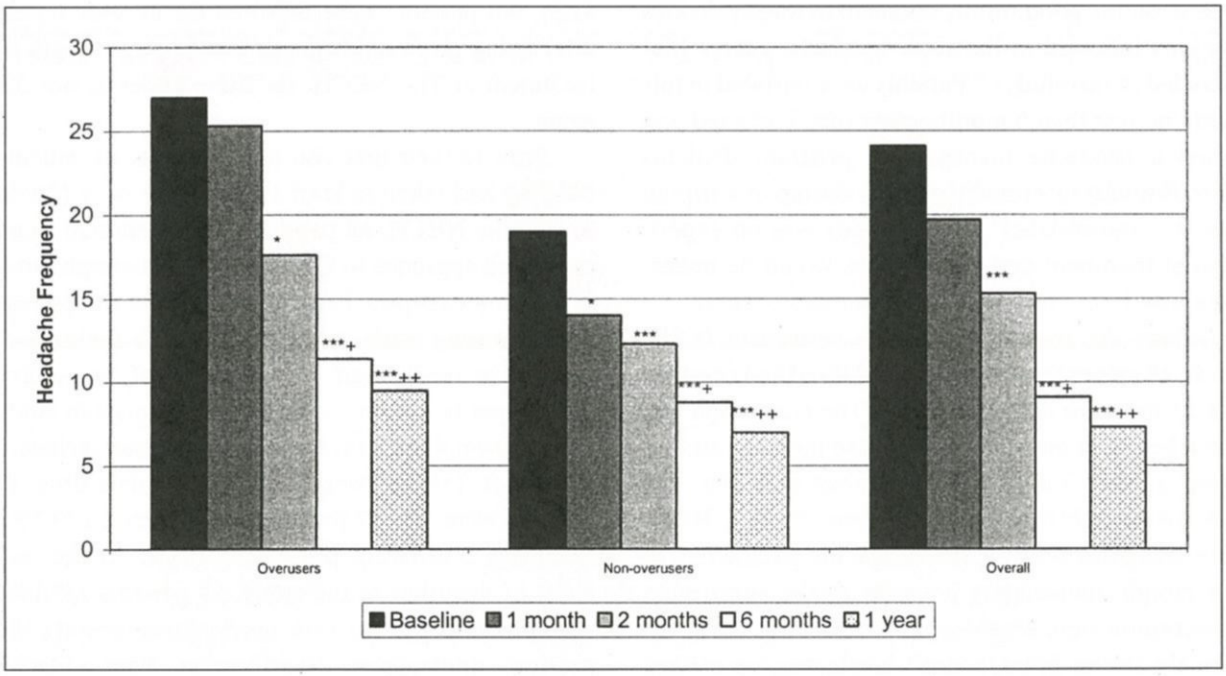

Fig. 1.—Comparison of the frequency of pain at baseline and after the start of daily naratriptan, overall and by groups of overusers and non-overusers of acute medication. ***$P<.001$ compared to baseline. +$P<.05$ versus 1 month. ++$P<.01$ versus 1 month.

Figure 1 compares the frequency of headache at baseline and after initiation of naratriptan therapy in those patients who were overusers and non-overusers of acute medications and overall. Overall, a statistically significant reduction of headache frequency was obtained in 2 months (15.3 days versus 24.1 days at baseline, $P<.001$), 6 months (9.1 days, $P<.001$), and 1 year (7.3 days, $P<.001$). Statistical significance also was reached between 6 months (9.1) and 1 month (19.7) ($P<.05$) and between 1 year (7.3) and 1 month (19.7) ($P<.01$). The same pattern was obtained in the overuser and non-overuser subgroups.

The mean number of severe attacks per month is presented in Figure 2. Overall, a significant reduction compared to baseline (12.5) was obtained in 1 month (5.6, $P<.01$), 2 months (5.7, $P<.01$), 6 months (2.8, $P<.01$), and 1 year (2.6, $P<.01$). The same pattern was verified in the overuser and non-overuser subgroups, the response being more evident in the non-overuser subgroup.

Figure 3 displays the headache index. Similar to the outcome frequency, a statistically significant reduction of the headache index was obtained in 2 months (33.0 versus 56.4 at baseline, $P<.001$), 6 months (19.5, $P<.001$), and 1 year (17.2, $P<.001$). Statistical significance also was reached between 6 months (19.5) and 1 month (42.2, $P<.05$) and between 1 year (17.2) and 1 month (42.2, $P<.01$). Again, the same pattern was obtained in both subgroups.

Of the 20 patients who continued to use naratriptan daily after 6 months of inclusion, 13 (65%) reverted to an episodic pattern of pain (migraine). At 1 year, 11 (55%) still continued to experience episodic headaches, 1 (5%) relapsed to CM, and 2 (10%) were lost to follow-up.

No patients were intolerant to naratriptan during the treatment period, and no one stopped treatment due to adverse events. There were no increased adverse effects to the occasional use of faster-acting triptans for severe breakthrough headache.

COMMENTS

Chronic migraine is the most frequently encountered headache syndrome at major tertiary care headache centers and, as reflected by their Migraine Disability Assessment (MIDAS) scores, patients with

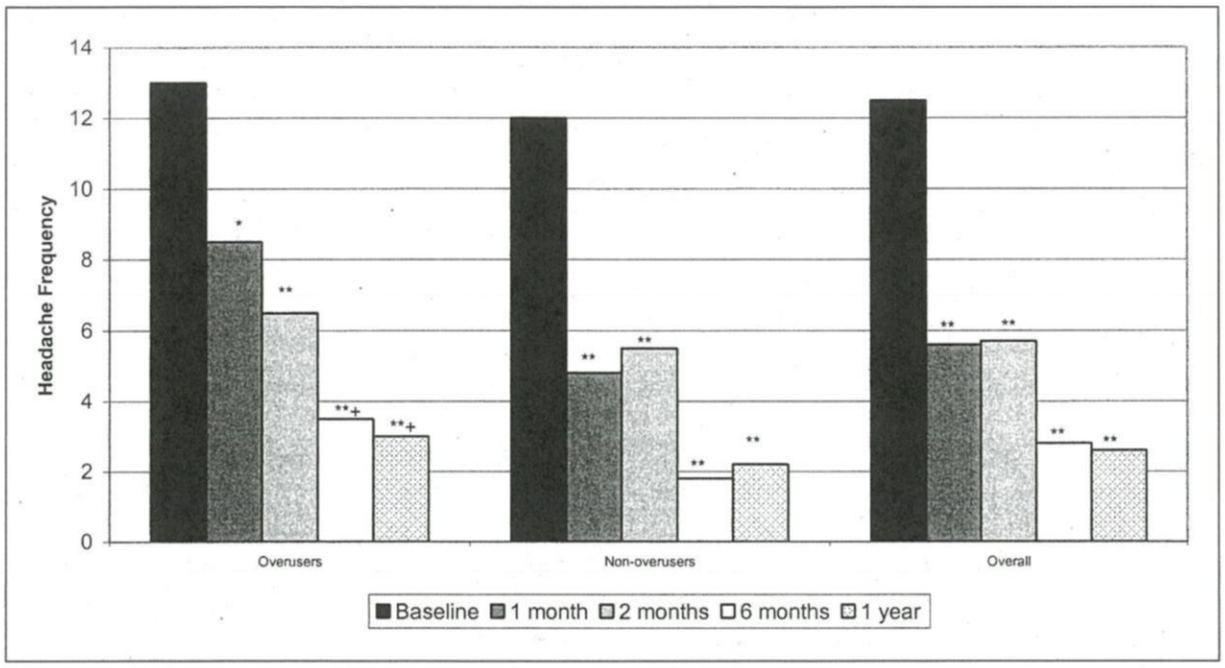

Fig. 2.—Comparison of the mean number of days per month with severe pain at baseline and after the start of daily naratriptan, overall and by groups of overusers and non-overusers of acute medication. *$P<.05$ compared to baseline. **$P<.01$ compared to baseline. +$P<.05$ compared to 1 month.

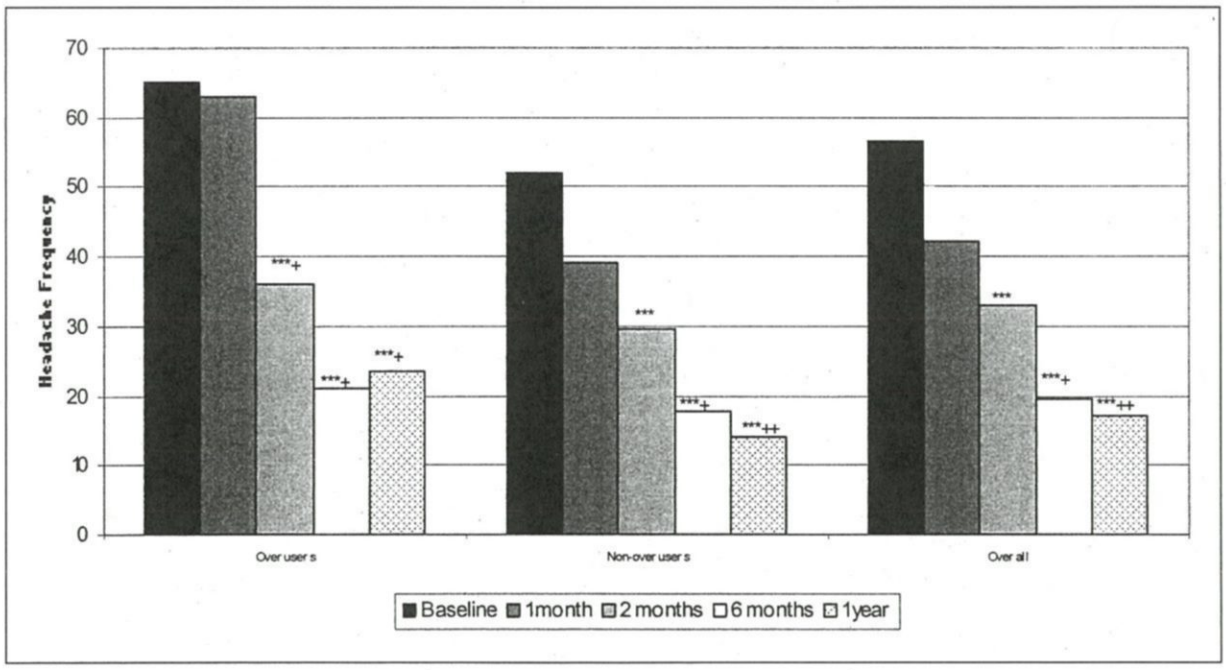

Fig. 3.—Comparison of the headache index at baseline and after the start of daily naratriptan, overall and by groups of overusers and non-overusers of acute medication. **$P<.001$ compared to baseline. +$P<.05$ versus 1 month. ++$P<.01$ versus 1 month.

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