Brief Communication

Naratriptan in the Preventive Treatment of Refractory Transformed Migraine: A Prospective Pilot Study

Fred D. Sheftell, MD; Alan M. Rapoport, MD; Stewart J. Tepper, MD; Marcelo E. Bigal, MD, PhD

Objective.—To assess the efficacy, safety, and tolerability of daily naratriptan in the preventive treatment of transformed migraine (TM) refractory to previous first line therapies.

Background.—Limited evidence suggests that the triptans can be used in the preventive treatment of refractory headaches.

Design/Methods.—We included subjects from 18 to 65 years old, with TM, with or without medication overuse (Silberstein and Lipton, 1996). All participants had previously failed at least two preventive medications. Concomitant, preventive medications were allowed if on a stable dose. After the baseline period, all patients received naratriptan 2.5 mg bid. The treatment phase lasted 3 months. The primary endpoint was change in headache frequency per month. Safety assessment included monthly ECGs, complete ophthalmologic exam, and monthly blood tests. Statistical analyses were performed using the intent-to-treat (ITT) population. We also conducted per-protocol (PP) analyses.

Results.—Our ITT population consisted of 30 subjects (79% female, mean age of 46.5 years). Mean headache frequency per month at baseline was 27.1 days and a significant reduction of headache frequency was obtained in 1 month (20.4, \( P < .001 \)), 2 months (18.9, \( P < .001 \)), and 3 months (19.0, \( P < .001 \)). HIT scores were 64.3 at baseline, 57.4 after 1 month (\( P < .001 \)), 55.7 after 2 months (\( P < .01 \)), and 60 at 3 months (\( P < .05 \)). The mean number of days using rescue medication was reduced from 17.7 at baseline, to 9.7 at 3 months (\( P < .001 \)). Our PP population consisted of 22 subjects, and 54% had fewer than 15 headaches per month at the end of the study (converted to an episodic pattern). No serious adverse events were reported. No significant changes were observed in blood pressure or in heart rate. ECGs and ophthalmologic exam were unchanged from baseline.

Conclusions.—(1) Daily use of naratriptan provided good preventive efficacy in an important subset of subjects with TM refractory to other preventive treatments. (2) The tolerability of this treatment was excellent. (3) Over a short period of time (3 months), no serious adverse events were reported, nor significant changes were found in the ECG or ophthalmologic evaluation.

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

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Limited evidence suggests that the triptans can be used in the preventive treatment of headaches refractory to first line therapies. Short-term or pulsed prevention with triptans is often used in women with menstrually related migraine.\(^1\),\(^2\) Additionally, a short course of daily triptans may be used as an adjunctive therapy in the process of detoxification of patients with transformed migraine (TM) and medication overuse.\(^3\),\(^5\)
TM, the most common subtype of the chronic daily headaches (CDH),6,7 is a syndrome not addressed in the International Classification of Headache Disorders.8 Patients with TM 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 associated symptoms becoming less severe.9-11 The treatment of TM often poses a major challenge for the clinician. Even when given the best expert care, a significant percentage of these patients still persist with daily or near-daily headaches.10,12-14

A recent published retrospective review of those with TM using naratriptan preventively for extended periods of time found that there was a statistically significant reduction in the frequency of headache days at 2 months, 6 months, and 1 year (P < .01 for all time points) after treatment was initiated. The tolerability reported in this study was excellent.15 However, the retrospective nature of the study as well as the potential for selection bias (incomplete identification of nonresponders) limits the generalization of these results. Consistently, herein we aim to prospectively assess the efficacy, safety, and tolerability of naratriptan in the preventive treatment of TM in patients who have been previously refractory to first line therapies.

METHODS

This is a prospective, open label study conducted in a tertiary care headache center. Inclusion criteria included:

1. Diagnosis of TM, with or without medication overuse, according to the criteria proposed by Silberstein et al.16
2. Previous failure to at least two adequate preventive medication trials.
3. Stable dose of preventive medications for at least 1 month (other preventive medications were allowed if on a stable dose for more than 30 days and still having frequent headaches).

We excluded subjects with known contraindications to triptans, and women during pregnancy and lactation. Ischemic abnormalities in the baseline ECG, as well as abnormal baseline ophthalmologic exam (conducted by an independent ophthalmologist), were also exclusion criteria.

All subjects with TM with medication overuse had failed to at least one detoxification protocol in the past. Subjects overusing acute medications were not included in this study if at least one detoxification trial was not conducted. Once in the study, we avoided detoxification programs (which would create important bias), but patients were allowed to reduce the consumption of their acute medication.

The baseline observation period consisted of 1 month, during which headache details were prospectively collected using headache calendars. After the baseline period, all patients received naratriptan 2.5 mg bid. Rescue medication consisted of an additional dose of naratriptan 2.5 mg or NSAIDs. The treatment phase lasted 3 months.

The primary endpoint for this study was change in headache frequency per month, comparing the third month and the baseline period. Secondary endpoint was the proportion of patients that converted to an episodic pattern of pain by 3 months. Other endpoints included change of headache frequency after 1 and 2 months of treatment, number of days with severe headache per month, change in Headache Impact Test-6 (HIT-6) scores per month, and headache score (frequency multiplied by severity assessed on a 4-point scale). Finally, we assessed the consumption of rescue medication per month.

Safety analyses included monthly measurements of blood pressure and heart rate, as well as monthly ECGs and blood tests. Complete ophthalmologic exam was conducted at baseline and at termination by an independent ophthalmologist.

Statistical analyses were performed on the intent-to-treat (ITT) population, using data subjected to the last observation carried forward algorithm. We also conducted separately per-protocol (PP) analyses in those who completed the entire study (completers). To compare several time points we used one-way analysis of variance after normality test. Two groups were compared with the paired t-test, assuming a 5% two tails significance level. Matched comparisons in nonparametric distributions were performed using the Friedman test with posttest.
This study received IRB approval and informed consent was obtained from all participants.

RESULTS

Our ITT population consisted of 30 subjects (79% female, mean age of 46.5 years). The PP population consisted of 22 subjects (77% female, mean age of 44.9 years). After 1 month, 28 patients remained in the study, 26 were in the study after the second month, and 22 completed the study. Of the 8 subjects (27%) that dropped out the study, 2 (7%) were lost to follow-up, 3 (10%) dropped out for lack of efficacy, and 3 (10%) due to adverse events (Fig. 1). A total of 20 patients (67% of our sample) were using one preventive drug when included in the study, while 10 (33%) were using two preventives. When enrolled, 15 (50%) were overusing acute medications.

ITT Analysis.—Mean number of headache days per month at baseline was 27.1, and a significant reduction of headache frequency was obtained at 1 month (20.4, $P < .001$), 2 months (18.9, $P < .001$), and 3 months (19.0, $P < .001$) (Fig. 2). No statistical differences were found comparing the three individual months of treatment with naratriptan.

Fig 1.—Flow of the study.

Fig 2.—Primary endpoint. Number of days with headache per month at baseline and after treatment.
Days with rescue medication use: 17.
HIT scores: 64.
Headache score: 54.
Number of days per month with severe pain: 7.
Number of days per month with any headache: 27.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (SD)</th>
<th>1 Month</th>
<th>2 Months</th>
<th>3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days per month with any headache</td>
<td>27.1 (3.4)</td>
<td>20.4 (8.9)**</td>
<td>18.9 (9.1)**</td>
<td>19.0 (8.7)**</td>
</tr>
<tr>
<td>Number of days per month with severe pain</td>
<td>7.5 (5.3)</td>
<td>3.8 (5.1)**</td>
<td>3.0 (3.6)**</td>
<td>4.0 (3.9)**</td>
</tr>
<tr>
<td>HIT scores</td>
<td>54.7 (11.3)</td>
<td>33.0 (12.1)**</td>
<td>36.2 (11.9)**</td>
<td>35.3 (11.5)**</td>
</tr>
<tr>
<td>Days with rescue medication use</td>
<td>64.3 (4.1)</td>
<td>57.4 (9.8)**</td>
<td>55.7 (11.2)**</td>
<td>60 (8.3)*</td>
</tr>
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</table>

Although the number of days using rescue medication was reduced with treatment overall ($P < .01$) at 1 and 2 months versus baseline, additional reduction in rescue medication consumption was observed after 3 months (5.7 days) versus 1 month (9.4 days), and 2 months (9.3 days) ($P = .043$).

Of those who finished the study, 55% ended with fewer than 15 headache days per month (converted to an episodic pattern). After 1 month, 38% had fewer than 15 headache days/month, and after 2 months 44% had fewer than 15 headache days/month (Fig. 3).

**T tolerability**: No serious adverse events were reported; 3 subjects (10%) withdrew from the study because of poor tolerability. Most common adverse events were drowsiness, tinnitus, and tiredness (6.7% each). Chest pain was observed in one subject (3.3%), while one other subject had chest tightness. Overall adverse events were reported by 20.6% of the subjects.

### Table 1.—Efficacy Endpoints as Assessed in the ITT Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (SD)</th>
<th>1 Month</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of days per month with any headache</td>
<td>27.1 (3.4)</td>
<td>18.3 (9.2)*</td>
<td>16.8 (8.9)*</td>
<td>18.4 (7.8)*</td>
</tr>
<tr>
<td>Number of days per month with severe pain</td>
<td>6.5 (4.5)</td>
<td>3.1 (4.9)*</td>
<td>2.7 (4)*</td>
<td>3.5 (3.9)*</td>
</tr>
<tr>
<td>HIT scores</td>
<td>54.7 (11.3)</td>
<td>29.0 (11.1)**</td>
<td>33.1 (10.3)**</td>
<td>32.4 (10.8)**</td>
</tr>
<tr>
<td>Days with rescue medication use</td>
<td>64.2 (4.5)</td>
<td>55.1 (9.6)*</td>
<td>52.7 (10.7)**</td>
<td>58.5 (8.6)*</td>
</tr>
</tbody>
</table>

* $P < .05$ versus baseline.
** $P < .01$ versus baseline.
*** $P < .001$ versus baseline.
† $P < .05$ versus 2 months.

The mean number of days with severe pain per month was reduced from 7.5 at baseline, to 3.8 at 1 month ($P < .01$), 3.0 at 2 months ($P < .001$), and 4.0 at 3 months ($P < .01$) (Table 1). No statistical differences were found comparing the three individual months of treatment. Table 1 also displays the headache scores and HIT-6 scores, both significantly reduced with treatment. Finally, the mean number of days using rescue medication was reduced from 17.7 at baseline, to 9.2 at 1 month ($P < .001$), 10.3 at 2 months ($P < .001$), and 9.7 at 3 months ($P < .001$).

**PP Analyses**: The results observed in our PP population are similar to those found in the ITT analyses and are summarized in Table 2. In brief, frequency was reduced from 27.1 days at baseline to 18.4 after 3 months ($P < .001$). Number of days with severe pain decreased from 6.5 to 3.5 ($P < .001$); HIT-6 scores decreased from 64.2 to 58.5 ($P < .001$). The headache score decreased from 54.7 to 34.2 ($P < .01$).

### Table 2.—Efficacy Endpoints as Assessed in the PP Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (SD)</th>
<th>1 Month</th>
<th>2 Months</th>
<th>3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days per month with any headache</td>
<td>27.1 (3.4)</td>
<td>18.3 (9.2)*</td>
<td>16.8 (8.9)*</td>
<td>18.4 (7.8)*</td>
</tr>
<tr>
<td>Number of days per month with severe pain</td>
<td>6.5 (4.5)</td>
<td>3.1 (4.9)*</td>
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<tr>
<td>HIT scores</td>
<td>54.7 (11.3)</td>
<td>29.0 (11.1)**</td>
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<td>Days with rescue medication use</td>
<td>64.2 (4.5)</td>
<td>55.1 (9.6)*</td>
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<td>58.5 (8.6)*</td>
</tr>
</tbody>
</table>
Fig 3.—Proportion of subjects with transformed migraine at baseline that converted to episodic headache with the treatment.

No significant changes were observed in blood pressure (systolic—120.6 mmHg at baseline vs. 121.8 mmHg after 3 months; diastolic—80.5 mmHg vs. 79.7 mmHg) or in heart rate (69.4 bpm vs. 70.7 bpm). ECGs and ophthalmologic exams were unchanged. Patients gained an average of 2.6 pounds during the treatment ($P < .05$) (Table 3).

**COMMENTS**

Most patients with TM benefit to some degree from treatment.$^{17,18}$ Patients suffering from long-duration TM can be, however, very difficult to treat, especially when the disorder is complicated by medication overuse, comorbid disease states, low frustration tolerance, depression, anxiety, and physical and emotional dependence.$^{18-20}$ There is a subgroup of patients that, despite optimized care, persist in a pattern of daily or near-daily headache, often overusing acute care medications.

There are few studies that have addressed the preventive treatment of TM as a distinctive subgroup of CDH. Most of these reports are anecdotal. Mathew and Ali$^{21}$ assessed the possible benefits of sodium valproate in consecutive CDH patients who were refractory to multiple standard treatments. Fifty-five percent had some degree of response and 10% discontinued medication due to side effects. Shuaib et al treated 37 patients with refractory migraine or CDH with topiramate (TPM) in an open-label study.$^{22}$ Thirty percent had what the authors classified as an excellent result, and 30% had a good result. The prevention of CDH with botulinum toxin type A,$^{23}$ zonisamide,$^{24}$ tizanidine (in a double-blind study),$^{25}$ and quetiapine$^{26}$ has also been studied.

Although naratriptan is not infrequently used in the short-term prophylaxis of menstrually related migraine, or as transitional therapy in the treatment of medication overuse headache, its efficacy in the preventive treatment of refractory headaches has been poorly studied. Anecdotal reports suggest its benefit in the treatment of TM.$^{15,27}$ Our study is a step forward in the discussion of the efficacy and safety of daily triptans in selected patients. Our data can be summarized as follows: (1) Daily naratriptan was effective in reducing the frequency of TM. (2) Naratriptan reduced the amount of severe pain and disability scores. (3) Although for most endpoints significance was reached after 1 month, and no additional benefits were observed in the subsequent months, in those who completed the study (PP population), additional reduction in rescue medication consumption was observed in the third month, compared to the first and second months. (4) Daily naratriptan was well-tolerated. No major side

**Table 3.—Vital Signs and Weight Comparing the Baseline Period and the Treatment Phase**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean (SD)</th>
<th>1 Month</th>
<th>2 Months</th>
<th>3 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>120.6 (8.8)</td>
<td>118 (12.8)</td>
<td>121.4 (11.9)</td>
<td>121.8 (12.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>80.5 (8.4)</td>
<td>81.6 (8.9)</td>
<td>83.3 (8.8)</td>
<td>79.7 (10.4)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>69.4 (12.7)</td>
<td>70.1 (14.3)</td>
<td>71.9 (14.7)</td>
<td>70.7 (13.4)</td>
</tr>
<tr>
<td>Weight</td>
<td>163.1 (31.6)</td>
<td>163.9 (31.2)</td>
<td>164.7 (27.4)</td>
<td>165.7 (31.9)*</td>
</tr>
</tbody>
</table>

* $P < .05$ versus baseline.
effects were observed, and few people dropped out of the study due to adverse events. No significant alterations in the ECGs, blood tests, and ophthalmologic evaluations were observed.

Several cautions must be taken when analyzing our results. First, although this is a prospective study, it is not controlled by placebo. It is a pilot, open-label study. Second, we included TM with and without medication overuse. Those overusing medication had failed detoxification protocols in the past. No patient stopped medication overuse during our study. Because studies show that preventive medication is often ineffective in patients overusing acute medication, we may have underestimated the benefits of naratriptan by including medication overusers. Third, it is also possible that as patients reduced their overuse of analgesics due to the beneficial effects of naratriptan, that this contributed somewhat to the efficacy noted in the later months of this study. Final and more important, as this was a short-duration study, we cannot adequately address the issue about whether naratriptan itself is inducing or could induce medication overuse in patients using it preventively. In the ITT population, the HIT-6 scores were significantly higher after 3 versus 2 months, which could suggest incipient effects of medication overuse, or, alternatively, that the preventive efficacy of naratriptan is transient. However, the amount of rescue medication used after 3 months was significantly less than after 2 and 1 months, which suggests the opposite. Additionally, more patients reverted to an episodic pattern of pain after 3 months, than after 1 or 2 months. The issue of naratriptan potentially inducing medication overuse if given preventively is, therefore, unanswered by our data. Long-term follow-up in these patients would be necessary. Reports suggest that if naratriptan is overused, it could induce medication overuse headaches.28,29 Conversely, it may be speculated that acute care medications given preventively daily in a scheduled manner (not prn in response to pain) would be less likely to induce medication overuse headache, possibly by avoiding continuous central sensitization, an hypothesis that also needs to be tested.

Our study has also strengths. Probably, the most relevant is that tolerability and safety were carefully assessed. Our findings support the concept that naratriptan is tolerable if given preventively, on a daily basis, for a relatively short (3-month) period. However, additional evidence is still necessary to support our results, since we had a short-term study with a restricted sample size. Long-term studies with a more robust sample size are necessary until the daily use of triptans may be suggested.

Based on this pilot study, we suggest that double-blind, placebo-controlled trials assessing the preventive efficacy of naratriptan in refractory headaches are warranted.

REFERENCES


