ABSTRACT

Tizanidine is an alpha2-adrenergic agonist perhaps best known as a muscle relaxant. Tizanidine has been investigated for the prevention of various types of headache, including chronic tension-type headache, chronic cluster headache, and tension-type headache. Results have been encouraging. The results reported here are from a double-blind, placebo-controlled study of 200 patients with chronic daily headache. The study assessed the efficacy of tizanidine as adjunctive prophylactic therapy. After baseline, 133 patients were eligible to continue on to randomization to tizanidine or placebo for 12 weeks. The target tizanidine dose was 24 mg given as a dose of 8 mg tid, or to the maximum dose tolerated. The mean dose tolerated was 18 mg. The results show dramatic differences in the headache index (the primary endpoint) and the number of severe headache days between the tizanidine and placebo groups. The headache index is defined as: (headache days x average intensity x duration in hours) / 28 days. Improvements were observed in all outcome measures, including patient-rated benefit with visual analog scales. There were no differences in efficacy for patients with chronic migraine compared to those with migrainous or chronic tension-type headache. Tizanidine was well tolerated. The results point to the potential importance of a central alpha2-adrenergic mechanism in the pathophysiology of chronic daily headache.

Tizanidine is an alpha2-adrenergic agonist that is perhaps best known as a muscle relaxant. It inhibits the release of norepinephrine at both spinal and supraspinal levels, including the locus ceruleus. It has no direct effect on the neuromuscular junction. Its antinociceptive effects are independent of the endogenous opioid system. For more than a decade, tizanidine has been investigated for the prevention of various types of headache, including chronic tension-type headache, chronic cluster headache, and tension-type headache, and the results have been encouraging. An open-label, dose-titration study of tizanidine for prophylaxis of chronic daily headache was conducted with 39 patients. The results showed statistically significant improvement in overall headache frequency, frequency of severe headaches, average headache intensity, peak headache intensity, and mean duration of headache, as well as an overall headache index based on frequency,
severity, and duration. Significant improvement also occurred in visual analog scales of overall headache status, mood, sleep, quality of life, sexual function, and measures of depression.\(^1\)

The results reported here are from a double-blind, placebo-controlled study of 200 patients with chronic daily headache to assess the efficacy of tizanidine as adjunctive prophylactic therapy. Patients included in the study had to have more than 15 days of headache per month for more than 3 months. They met the International Headache Society (IHS) criteria for migraine, migrainous headache, or tension-type headache.\(^6\) This cohort underwent a 4-week, single-blind, placebo baseline and was then re-evaluated. Those who had fewer than 15 headaches during the baseline phase were excluded to eliminate placebo responders and to verify that the headaches met IHS criteria. As a result, 134 of the 200 patients were eligible to continue in the study. One patient decided not to continue, leaving 133 patients who were randomized to receive either tizanidine (tzd) or placebo (pcb). Of those randomized patients, 92 (tzd = 45, pcb = 47) completed at least 8 weeks of treatment and they were included in efficacy analyses. A total of 85 patients completed the entire 12 weeks of planned treatment (tzd = 44, pcb = 41).

The demographics of the study were similar to recent epidemiological data of people with chronic daily headache: mean age of approximately 40 years, female to male ratio of approximately 4:1. Over one half of the patients had a history of chronic headache of more than 5 years. About three fourths of the cohort (77%) had IHS migraine, while 23% had either migrainous or chronic tension-type headache.

During the treatment phase, tizanidine was gradually titrated over 4 weeks to a target dose of 24 mg per day (given as 8 mg tid), or to the maximum tolerable dose. Tolerable doses ranged from 2 mg per day to 24 mg per day, with a mean tolerable dose of 18 mg. One half of the tizanidine group received 20 mg of tizanidine or more per day. Patient tolerability varied. The maximum dose was maintained during weeks 5 to 12.

The results show the most dramatic differences in the headache index (the primary endpoint) and the number of severe headache days between the tizanidine and placebo groups (Table 1). The headache index is defined as (headache days x average intensity x duration in hours)/28 days. Of note, the tizanidine group showed significant improvement on all outcome measures.\(^1\)

### Table 1. Mean Percentage Reduction in Headache Measures During the Last 4 Weeks of Treatment, Compared With Single-Blind Placebo Baseline

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Tizanidine (n = 45)</th>
<th>Placebo (n = 47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache index</td>
<td>54%</td>
<td>19%</td>
<td>.014</td>
</tr>
<tr>
<td>Severe headache days</td>
<td>55%</td>
<td>21%</td>
<td>.033</td>
</tr>
<tr>
<td>Peak headache intensity</td>
<td>35%</td>
<td>20%</td>
<td>.011</td>
</tr>
<tr>
<td>Average headache intensity</td>
<td>33%</td>
<td>20%</td>
<td>.028</td>
</tr>
<tr>
<td>Headache duration</td>
<td>35%</td>
<td>19%</td>
<td>.014</td>
</tr>
<tr>
<td>Total headache days</td>
<td>30%</td>
<td>22%</td>
<td>.059</td>
</tr>
</tbody>
</table>

\*Adverse events reported here are those reported by >10% of the tizanidine patients and were the only adverse events that were statistically significantly different between the 2 treatment groups. Data adapted from Lake AE, Saper JR, Winner P, et al.\(^9\)
measures, with total headache days approaching significance. Based on results from visual analog scales, patients rated themselves as significantly better with tizanidine treatment administered at the end of the single-blind placebo phase and each 4 weeks of treatment ($P = 0.0069$). There were no differences in efficacy for patients with chronic migraine compared with those with migraineous or chronic tension-type headache.

Tizanidine was generally well tolerated (Table 2). A total of 4 patients (tzd = 2; pcb = 2) experienced serious adverse events; 13 patients discontinued treatment due to adverse events (tzd = 9; pcb = 4). These differences were not statistically significant. Only 1 tizanidine-treated and 1 placebo-treated patient had elevated liver enzymes, which returned to normal with drug discontinuation.

Patients were excluded from the study if they were using analgesics as abortive medication for their migraines more than 3 days per week. The mean number of analgesic days per week during baseline was less than 2 (tzd = 1.8; pcb = 1.7). The use of analgesics over the course of the study did not change, although a slight decrease was noted in both groups. However, the observed headache reductions were not related to discontinuation of excessive medication use or to more frequent use of analgesics during treatment. Because this was tested as an adjunctive therapy, the effect of tizanidine on the efficacy of any specific medication (abortive or prophylactic) requires further study.

These results show that tizanidine can have a significant benefit as an adjunct prophylactic treatment for chronic daily headache. It can reduce the overall headache index and the frequency of severe headaches in particular, and it may increase the efficacy of abortive medications. The results point to the possible importance of a central alpha2-adrenergic mechanism in the pathophysiology of chronic daily headache. The prophylactic effect may be due to mitigation of central sensitization in migraine, resulting in greater reductions in headache severity and duration than in the total number of headache days. A report describing the study in detail will be published later this year.

REFERENCES