An Open-Label Dose-Titration Study of the Efficacy and Tolerability of Tizanidine Hydrochloride Tablets in the Prophylaxis of Chronic Daily Headache

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Objective.—To assess effectiveness and safety of tizanidine hydrochloride tablets for the prophylaxis of chronic daily headache.

Background.—Tizanidine hydrochloride is an α_2-adrenergic agonist that inhibits the release and effectiveness of norepinephrine at both central sites (eg, the locus ceruleus) and the spinal cord. It acts as a central muscle relaxant and has antinociceptive effects. Preliminary research and retrospective analyses have suggested efficacy in treatment of both chronic tension-type headache and chronic daily headache with migrainous features.

Design.—Thirty-nine patients with more than 15 headache days per month (33 with migraine, 5 migrainous, 1 chronic tension-type) completed a 4-week baseline, with 31 completing a planned 12 weeks of treatment with tizanidine. Dosing was titrated from 2 mg at bedtime to a median daily dose of 14 mg (mean, 13.5; SD, 4.3; range, 4 to 20, divided over three doses per day) by treatment week 4.

Results.—The overall headache index through week 12 (headache frequency × average intensity × duration) declined significantly ($P<.00000002$), with a corresponding increase in mean percentage improvement from 49% for weeks 1 through 4, to 65% for weeks 5 through 8, and 64% for weeks 9 through 12 ($P<.0182$). During weeks 9 through 12, 67% had improved more than 50% compared to baseline. Overall headache frequency declined from 22.83 to 15.83 days per month ($P<.00001$), with frequency of severe headaches dropping from 7.52 to 3.58 days per month ($P<.000035$). Average headache intensity dropped from 1.83 to 1.07 (1-to-5 scale), peak intensity declined from 2.37 to 1.40, and mean duration was reduced from 6.96 to 4.00 hours per headache ($P<.00001$). Improvement also occurred on visual analog scales of overall headache status, mood, sleep, quality of life ($P<.00001$), and sexual function ($P<.0075$); as well as the Beck Depression Inventory-II ($P<.00073$).

Mild-to-moderate adverse events reported by more than 10% of the patients included somnolence, asthenia, and dry mouth. Only 3 patients discontinued treatment due to adverse events: somnolence and dry mouth alone (n = 1), or in combination with either hyperkinesis (n = 1) or constipation (n = 1). One patient had elevated liver enzymes that returned to normal after the drug was discontinued.

Conclusions.—The results provide preliminary support for the efficacy, safety, and tolerability of tizanidine in the prophylaxis of chronic daily headache.

Key words: chronic daily headache, efficacy, migraine, open-label study, prophylaxis, tizanidine, tolerability

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Tizanidine hydrochloride (HCl) is an α_2-adrenergic agonist that inhibits the release and effectiveness of norepinephrine at both the brain stem (eg, the locus ceruleus) and the spinal cord.[1] It acts as a central muscle relaxant, and was initially approved in the United States for the treatment of spasticity associated with multiple sclerosis and spinal cord injury.[2] Animal studies have also shown tizanidine to have a direct antinociceptive effect, with a potency from per-oral administration similar to that of subcutaneously administered morphine.[3] The antinociceptive effect has been demonstrated at doses below those required

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to produce muscle relaxation,[3] does not involve the endogenous opioid system,[4] and appears to be centrally mediated by α_2-adrenoreceptors, with little if any interaction with serotonin, dopamine, or GABA receptors.[5]

Double-blind, placebo-controlled, randomized designs have shown tizanidine to significantly reduce acute low back pain.[6-7] Tizanidine was found to be as effective as diazepam in reducing acute cervical muscle spasm and associated pain.[8] A double-blind, placebo-controlled, randomized study demonstrated a significant clinical effect for tizanidine in chronic tension-type headache,[9] with an open-label study finding significantly higher plasma 3-methyoxy-4-hydroxyphenylglycol (MHPG) levels in those patients with tension-type headache who had the best headache response.[10] A recent, large-scale, clinical study reported very good results in 222 patients with either chronic tension-type headache or chronic daily headache with coexistent migraine.[11] The clinical literature also suggests potential efficacy in the treatment of chronic cluster headache[12] and trigeminal neuralgia.[13]

Clinical studies note a superior overall tolerability profile for tizanidine compared to other antispasticity agents such as baclofen and diazepam, with fewer complaints of weakness.[1,14] The most commonly reported adverse events include dry mouth, drowsiness, and dizziness. Other side effects that occur more frequently with tizanidine than placebo conditions include asthenia, hypotension, elevated liver enzymes (reversible on drug discontinuation), nausea, speech difficulties, and dyskinesia.[1]

These data suggest that tizanidine might be an effective and safe prophylactic agent for the treatment of chronic daily headache, including those patients whose frequent headaches include intermittent severe migraine. Patients with persistent chronic daily headache are the most likely group of individuals with headache to seek treatment at specialized headache centers.[15-17] Clinical samples of patients with chronic daily headache are predominantly weighted toward those whose headaches include migrainous features.[17-19]

This open-label study was designed as a prospective pilot investigation of the efficacy, tolerability, and safety of tizanidine tablets in the prophylaxis of chronic daily headache (ie, more than 15 days of headache per month), utilizing the diagnostic criteria suggested by Silberstein and others.[20]

SUBJECTS AND METHODS

Objectives.—The primary objective was to assess the efficacy of tizanidine for prophylaxis of chronic daily headache by evaluating changes in headache diary data: headache frequency, severity, and duration, as well as the combination of these measures in a headache index. Secondary objectives were to assess changes in visual analog scale measures of overall headache status, sleep, mood, sexual function, and quality of life, as well as depression using a standardized psychometric measure. Safety objectives included the identification of adverse events, including their significance and severity, based on patient diaries, interviews, and changes in laboratory measures.

Outcome Measures.—Patients recorded peak and average levels of headache severity each day using a 6-point scale, as follows: 0 = no headache; 1 = mild headache, easily ignored; 2 = mild plus, bothersome discomfort; 3 = moderate, painful; 4 = moderate-severe, very painful; and 5 = severe, intensely painful. Headache duration was recorded as the number of hours of headache each day. Peak level of functional impairment was recorded with a 4-point scale (0 = able to perform normally, 1 = ability to function mildly impaired, 2 = ability to function moderately impaired, 3 = ability to function severely impaired). Patients also recorded the dose of tizanidine (ie, the number of scored 4-mg tablets) for each of three daily doses in the diary, as well as the name and dose of rescue medications. Visual analog scales consisted of five 100-mm lines, with one line each for overall headache status, sleep, mood, quality of life, and sexual function. Each line was anchored at 0 ("extremely bad") and 10 ("extremely good"). Changes in psychological status (depression) were evaluated using the Beck Depression Inventory-II.[21]

Inclusion Criteria.—Eligible participants included men or women patients between the ages of 16 and 65 years who reported at least 15 days of headache per month for at least 3 months prior to entry. Headaches could include intermittent severe migraine as well as mild to moderate migrainous or tension-type headache. Patients were then required to adequately com-

plete a 4-week headache diary. Only those patients whose diaries showed at least 15 days of headache in 4 weeks were permitted to start tizanidine and continue for the remainder of the study.

Exclusion Criteria.—Patients with severe neurological accompaniments, prolonged aura, or migrainous infarction were excluded. Other illness-related exclusion criteria included any medical disorder or previous surgery that might interfere with absorption, metabolism, or excretion of the study drug; severe, debilitating concurrent medical conditions (eg, coronary artery disease, renal failure, hepatic failure, systemic cancer); or any clinically significant abnormality in clinical laboratory tests at screening, such as evidence of significant renal insufficiency (serum creatinine greater than 2 mg/dL), impaired liver function (SGOT or SGPT more than twice the upper normal limit), or severe, uncontrolled systemic hypertension (systolic blood pressure [BP] above 180 mm Hg, diastolic BP above 110 mm Hg). Patients with any neuropsychological problem, impaired speech/language function, or unreliable social situation that might interfere with their ability to adequately complete the study were also excluded.

Medication-related exclusion criteria included previous failed treatment with three or more preventative medications given in adequate doses; use of analgesic, symptomatic, or migraine abortive medications more than 3 days per week within the past 2 weeks; participation in any investigative drug study in the previous month; drug dependence, narcotic tolerance, or any history of drug or alcohol abuse within the past 2 years; or current use of α_2-adrenergic agonists or drugs with α_2-adrenergic receptor-blocking properties. However, at the discretion of the investigator, very limited use of promethazine or hydroxyzine was allowed for control of nausea, if necessary. Women who were pregnant, breast-feeding, or sexually active and of childbearing potential who were not using medically accepted means of contraception were also excluded.

Patients were required to continue other permissible concurrent preventative/prophylactic medications (ie, those with no known α_2-adrenergic impact) at a stable dose between the screening and baseline visits, as well as throughout the study. Permissible analgesic/abortive/rescue medications included simple analgesics (ie, aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs) and migraine abortives (ie, ergots, isometheptene, triptans). Once enrolled, patients were prohibited from adding any new medications to their program, or they would be discharged from the study.

Patients.—A total of 43 patients were initially enrolled in the study. After conclusion of the baseline records, 39 continued to meet inclusion/exclusion criteria and started treatment with tizanidine. The sample consisted of 38 women and 1 man, with a mean age of 39.08 years (SD, 13.40; median, 36; range, 17 to 65 years). Thirty-three (85%) met the International Headache Society (IHS) criteria for migraine (IHS 1.1 or 1.2), 5 (13%) had migrainous headaches (IHS 1.7), and only 1 met the criteria for chronic tension-type headache without coexisting migraine (IHS 2.2).[22]

All patients initially reported between 4 to 7 days of headache per week for at least 3 months prior to entering the study. The majority of patients (n = 34, 87%) reported at least 1 year of chronic daily headache, with 26 (67%) reporting at least a 3-year history, and 22 (56%) reporting 5 years of more than 15 days of headache per month. Fourteen (36%) of the 39 patients reported constant head pain, and 25 (64%) reported intermittent headache.

Initial baseline headache records over a 4-week (28-day) period indicated a mean of 22.74 days of headache (SD, 4.86; median, 24; range, 15 to 28). On average, patients recorded about 2 days of severe headaches per week, or about 7 days of severe headache in the 28-day baseline (mean, 7.87; SD, 5.93; median, 7; range, 0 to 26). All patients met the inclusion criteria of at least 15 days of headache during the 28-day baseline.

Design.—This was an open-label study with a 4-week baseline, followed by 12 weeks of scheduled three-times-a-day treatment with tizanidine. Patients meeting initial entry criteria underwent screening evaluations, signed the informed consent, and received instructions to complete a daily diary for 1 month. One month after the screening visit, patients returned for the baseline visit for further evaluation and qualification. Patients meeting baseline inclusion criteria completed any additional baseline evaluations, and were given instructions to begin the study

medication the next day (day 1). Patients returned at weeks 4, 8, and 12 to review completed diaries, assess adverse events, take vital signs, assess concomitant medication, reconcile diary reports of tizanidine dosing with the amount of remaining medication, and receive sufficient tizanidine for the next 4-week interval. Interim telephone contacts to discuss headache status, adverse events, diary compliance, drug management, and concomitant medications were scheduled at 2-week intervals between each interview visit.

Screening laboratory tests occurred at the first screening visit, with a repeat of the urine pregnancy test at the end of baseline prior to starting treatment. Follow-up laboratory tests were completed at weeks 4 and 12. Patients completed the visual analog scales at the initial screening, at the end of baseline before starting treatment, and then at weeks 4, 8, and 12. The Beck Depression Inventory-II was completed at the initial screening and week 12.

Medication Protocol.—The tizanidine dose was slowly escalated over approximately 4 weeks, starting with half of a 4-mg tablet (2 mg) at bedtime and titrating upward to the maximum tolerated dose or a maximum daily dose of 18 mg, divided over three dose intervals per day. Patients remained on the maximum tolerated dose for the remainder of the study. Further modifications in dosing were based on tolerability. The mean total daily dose of tizanidine at week 4 was 13.77 mg (SD, 3.99; median, 15; range, 4 to 18), 13.62 mg at week 8 (SD, 4.25; median, 15; range, 4 to 18), and 13.51 mg at week 12 (SD, 4.29; median, 14; range, 4 to 20). One patient violated the protocol limit of 18 mg and increased the dose to 20 mg during the final week of treatment. Patients then tapered off tizanidine over a 1-week period and were scheduled to return at week 13 for safety evaluations and to return study medication.

Statistical Analysis.—Means for the average level of headache, peak level of headache, peak level of impairment, and headache duration were calculated for each of the four treatment periods (baseline, weeks 1 through 4, weeks 5 through 8, weeks 9 through 12). The number of days with any headache (levels 1 to 5) and severe headache (ie, those headaches with a peak severity of 4 to 5) were standardized to a 28-day period. Use of analgesic/abortive medication was standardized to the mean number of days per week.

Using the daily patient diary entries, two headache indices were computed as follows: (1) overall headache index = headache frequency × average intensity × duration/28 days, and (2) peak headache index = headache frequency × peak level/28 days. The percentage reduction in headache frequency and the two headache indices compared with baseline was computed as: ([baseline headache measure − treatment period measure]/baseline measure) × 100. For statistical analysis based on the percentage of improvement in the headache index, any patient whose headaches deteriorated during the treatment period was assigned an index of "0" to avoid negative numbers.

Pre-post comparisons of all outcome measures (daily patient diary measures including headache indices, visual analog scales, Beck Depression Inventory-II) were made using appropriate inferential statistics (eg, analysis of variance for repeated measures) using Systat 8.0 for Windows.[21] In order to minimize the likelihood of spurious findings of significance, the acceptable probability levels for statistical significance were determined using the Bonferroni correction. Based on a total of 15 planned outcome measures (7 direct daily headache diary measures + 2 composite headache index measures + 5 visual analog scales + 1 Beck Depression Inventory-II = 15), a probability level of $P<.0033$ ($P<.05$ divided by 15 planned comparisons) was utilized as the level of clinical significance in the overall analyses.

If the overall analysis for repeated measures was significant, then post hoc comparisons of one time period to the next were made using paired *t* tests, in order to determine the point at which therapeutic changes became significant and whether there was evidence for continued significant improvement during successive 4-week intervals of treatment. The complete repeated-measures analysis was, by necessity of the measure, limited to those patients who completed 4 weeks of baseline and all 12 weeks of tizanidine. However, post hoc comparisons of one period to the next could be completed with the number of patients who had completed each successive period. For three planned comparisons (baseline versus weeks 1 through 4, weeks 1 through 4 versus weeks 5 through 8, weeks 5 through 8 versus weeks 9 through 12), the acceptable significance level was $P<.0167$

Table 1.—Headache Diary Data

	Baseline (n = 39)	Weeks 1 Through 4 (n = 38)	Weeks 5 Through 8 (n = 33)	Weeks 9 Through 12 (n = 30)
Frequency of headache*				
Median	24	19	16	14.5
Mean (SD)	22.74 (4.86)	19.16 (7.26)	16.67 (8.82)	15.83 (9.27)
Frequency of severe headache*				
Median	7	4	2	2
Mean (SD)	7.87 (5.93)	4.79 (4.21)	3.05 (3.85)	3.70 (4.62)
Average level of headache intensity per day (0 to 5)				
Median	1.7	1.2	0.9	1.1
Mean (SD)	1.86 (0.65)	1.38 (0.61)	1.09 (0.68)	1.09 (0.81)
Peak level of headache intensity per day (0 to 5)				
Median	2.3	1.8	1.3	1.4
Mean (SD)	2.4 (0.86)	1.8 (0.83)	1.43 (0.85)	1.42 (0.99)
Duration of headache, hours per day				
Median	4.9	3.5	2.1	2.1
Mean (SD)	6.86 (4.88)	5.56 (5.01)	4.09 (4.52)	4.02 (4.17)
Overall headache index†				
Median	7.5	3.0	1.1	1.5
Mean (SD)	13.2 (14.4)	9.2 (12.8)	6.1 (10.4)	6.0 (10.3)
Peak headache index‡				
Median	1.7	1.1	0.8	0.7
Mean (SD)	2.0 (1.0)	1.4 (1.1)	1.1 (1.0)	1.1 (1.1)
Level of headache-related impairment per day (0 to 3)				
Median	0.9	0.7	0.4	0.3
Mean (SD)	1.1 (0.8)	0.8 (0.6)	0.6 (0.5)	0.6 (0.7)
Use of abortive/analgesic medication, days per week				
Median	2	1.5	1	1.4
Mean (SD)	1.7 (1.2)	1.4 (0.9)	1.2 (1.0)	1.4 (1.2)

*Total number of headache (and severe headache) days in 4-week interval.
†Overall headache index = (headache frequency × average intensity × duration)/28 days.
‡Peak headache index = (headache frequency × peak level of intensity)/28 days.

($P<.05$ divided by three planned comparisons). If there were only two planned comparisons, as in the case of comparing percentage improvement during the three 4-week treatment periods, acceptable significance was $P<.025$ ($P<.05$ divided by two comparisons).

In most cases, visual and statistical examination of the measures met criteria for a normal distribution, and statistical analysis relied on parametric measures (eg, analysis of variance). However, if either the interval of skewness or kurtosis ± 2 times its standard error (SES or SEK) did not include zero, then the assumption of normality was rejected.[21] If this were the case, the Friedman test, a nonparametric analog of the analysis of variance or *t* test (depending on the number of related comparisons), was utilized as the more appropriate test statistic.

In addition, the number of treatment responders was identified. A responder was defined as any patient with a reduction in headache frequency or headache index of at least 50% comparing the baseline period (week −4 through week −1) with a given treatment period (eg, week 8 to week 12). The percentage of responders was defined in three ways: (1) as a percentage of patients who completed 4 weeks of baseline data and 4 weeks of treatment, (2) as a percentage of those who completed 8 weeks of treatment, and (3) as a percentage of those who completed all 12 weeks of treatment.

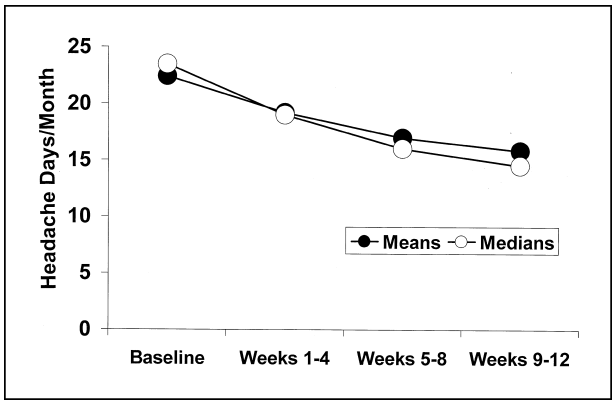

Fig 1.—Frequency of headache: total headache days in 4-week interval.

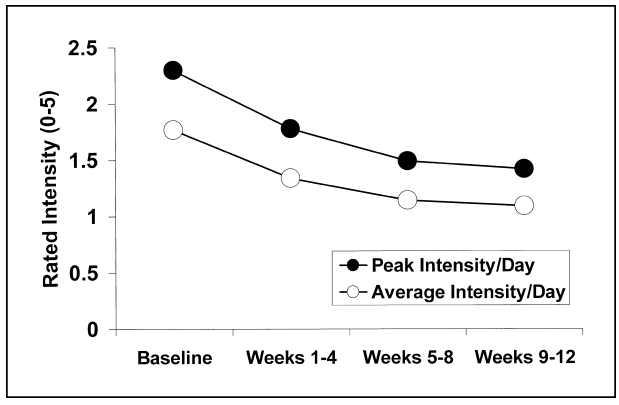

Fig 3.—Mean levels of headache intensity rated on a 6-point scale: 0 = no headache; 1 = mild headache, easily ignored; 2 = mild plus, bothersome discomfort; 3 = moderate, painful; 4 = moderate-severe, very painful; 5 = severe, intensely painful.

RESULTS

Disposition of Patients.—Of the 39 patients who started tizanidine, 38 (97%) continued treatment at least 4 weeks, 33 (85%) continued at least 8 weeks, and 30 (77%) continued through the planned 12 weeks of treatment. Five patients discontinued treatment for reasons unrelated to the study drug (eg, development of tooth disease and an infection rated as mild). One patient was lost to follow-up at week 12. Three patients (7.7%) chose to discontinue treatment due to adverse events rated as mild to moderate.

Safety and Tolerability.—The 3 treatment dropouts due to adverse events each reported somnolence and dry mouth, in combination with hyperkinesis in 1 patient and constipation in another. Common and generally mild to moderate adverse events possibly related to tizanidine and reported by 10% or more of the patients included somnolence (n = 17, 42.5%), asthenia (n = 14, 35.0%), dry mouth (n = 10, 25.0%), and dizziness (n = 4, 10.0%). Only 2 patients reported possibly related adverse events that were rated as severe: somnolence (n = 1) and 1 day of severe migraine (n = 1). Both chose to continue treatment until the conclusion of the planned 12 weeks, and the patient with the day of severe migraine exhibited overall improvement over the course of the study.

One patient, a 50-year-old white female (height, 64 inches; weight, 182 lb), showed elevation in liver enzymes (SGOT = 133 U/L, SGPT = 320 U/L) during the last hepatic laboratory assessment, 77 days after the start of treatment at a mean daily dose of 11.6 mg. Liver enzymes returned to normal limits when reassessed 39 days later after the conclusion of the study. All other lab values and vital signs for enrolled patients remained within acceptable limits. There were no deaths or other serious adverse events.

Headache Diary Measures.—Table 1 shows headache diary data for each measure during the four experimental phases (baseline, weeks 1 through 4, weeks 5 through 8, and weeks 9 through 12) based on the number of patients who completed each phase. Figures 1 through 8 graphically illustrate changes in each headache measure for the 30 patients who remained on tizanidine and successfully completed study requirements through week 12.

All headache diary measures improved significantly after patients started tizanidine, including the

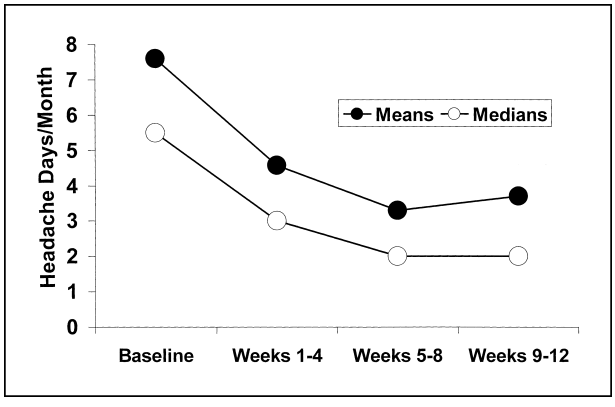

Fig 2.—Frequency of severe headache: total severe headache days in 4-week interval.

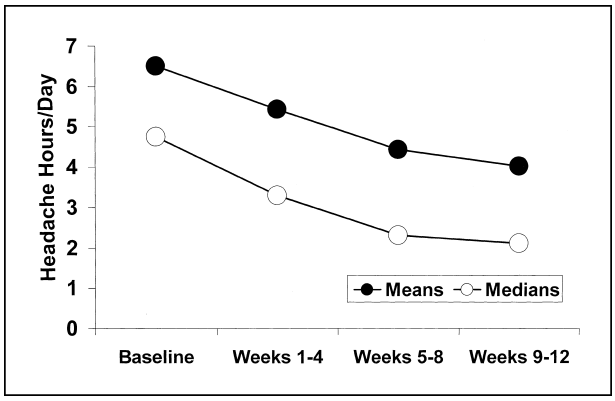

Fig 4.—Duration of headache.

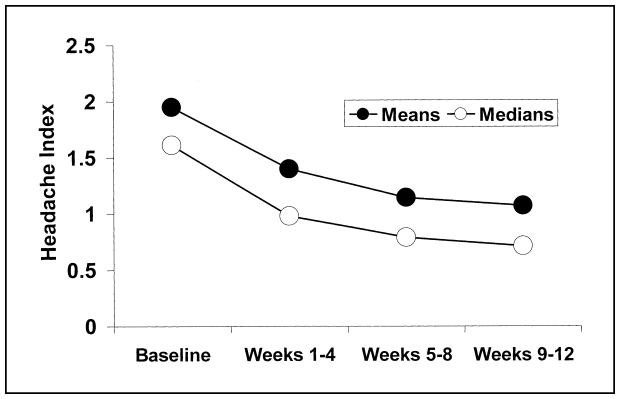

Fig 6.—Peak headache index, calculated as (frequency × peak intensity)/28 days.

total number of headache days per treatment period ($P<.00001$); days with severe headaches ($P<.000035$); average level of headache intensity, peak level of headache intensity, duration of headache (all at $P<.00001$); use of rescue medication ($P<.0015$); and peak level of headache-related impairment ($P<.000033$). Post hoc analyses indicated that significant headache improvement occurred on each measure during the first 4 weeks of treatment. Additional significant improvement occurred during weeks 5 through 8 versus weeks 1 through 4 for the frequency of severe headaches, average level of headache intensity, peak level of headache intensity, duration of headache, and peak level of headache-related impairment. In addition, the overall frequency of headaches ($P<.0186$) and the use of abortive/analgesic medications ($P<.0177$) for the comparisons of weeks 1 through 4 and weeks 5 through 8 fell only slightly short of the required $P<.0167$ level of significance based on the Bonferroni correction.

For those who completed the study, the frequency of headaches (Figure 1) declined from a mean of 22.4 days during the 28-day baseline period (SD, 5.3; median, 23.5) to a mean of 15.8 days during weeks 9 through 12 (SD, 9.3; median, 14.5), a difference of 6.6 days (based on the mean) and 9 days (based on the median). The frequency of severe headaches declined from a mean of 7.6 days (SD, 6.4; median, 5.5) to a mean of 3.7 days (SD, 4.6; median, 2), a difference of 3.9 severe headache per 28 days (based on the mean) and 3.5 days (based on the median)—a decline of about 1 severe headache day per week. The duration of headache (Figure 3) decreased from a mean of 7.0

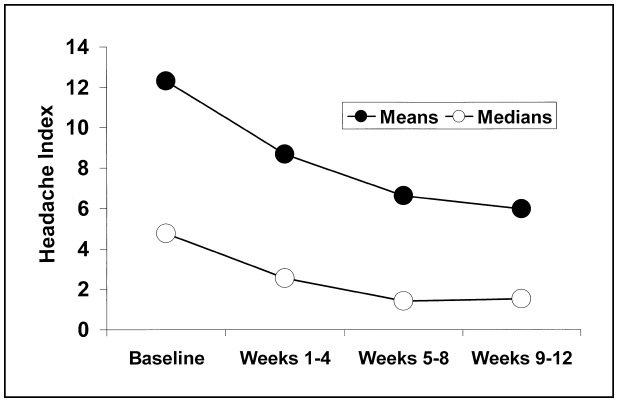

Fig 5.—Overall headache index, calculated as (frequency × average intensity × duration)/28 days.

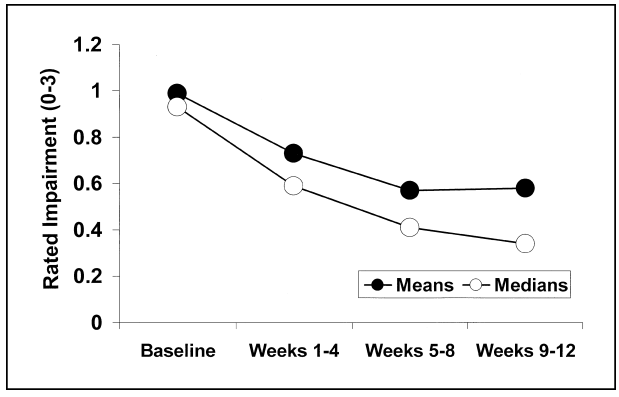

Fig 7.—Level of headache-related impairment per day rated on a 4-point scale: 0 = able to perform normally, 1 = ability to function mildly impaired, 2 = ability to function moderately impaired, 3 = ability to function severely impaired.

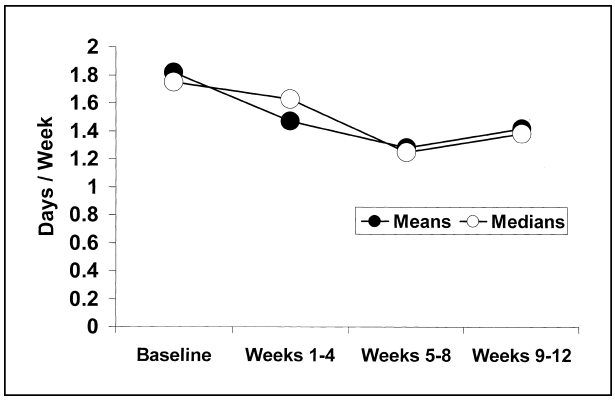

Fig 8.—Use of abortive/analgesic medication.

hours per day during baseline (SD, 4.8; median, 5) to a mean of 4.0 hours during weeks 9 through 12 (SD, 4.2; median, 2.4).

The headache index (Figures 4 and 5) can perhaps be considered the best overall measure of headache activity, due to its combination of frequency, intensity, and duration measures. The overall headache index (based on headache frequency×average intensity× duration) showed a highly significant overall improvement ($P<.00000002$). Improvement initially emerged during weeks 1 through 4 ($P<.000099$), with further improvement during weeks 5 through 8 ($P<.000063$). The peak headache index (based on headache frequency × peak intensity of headache per day) also showed a high level of overall significance ($P<.00001$). As with the overall headache index, improvement was demonstrated during the first 4 weeks of treatment ($P<.000009$), with continued improvement when weeks 5 through 8 were compared with weeks 1 through 4 ($P<.0123$).

While the use of abortive/analgesic medication did show a statistically significant decline compared to baseline, the magnitude of the differences was less clinically significant than was the case for the other diary measures. Abortive/analgesic use dropped from a mean of 1.8 days per week during the baseline period (SD, 1.0; median, 1.8) to 1.4 during weeks 9 through 12 (SD, 1.2; median, 1.4). In general, patients did not use abortive/analgesic medication frequently, even during the baseline phase.

Percentage Improvement in Headache.—Percentage improvement data is shown in Table 2. The mean percentage improvement during the first 4 weeks of treatment based on the overall headache index was 48.7% (SD, 33.7; median, 53.2). This increased to 65.3% during weeks 5 through 8 (SD, 34.6; median, 81.5) and was maintained at roughly the same level during weeks 9 through 12 (mean, 63.5%; SD, 35.9; median, 75.4). There was an overall trend toward significant increase in percentage improvement during the course of the study ($P<.018$), primarily due to the increase in percentage improvement during weeks 5 through 8 compared to weeks 1 through 4 ($P<.012$).

The mean percentage improvement in the peak headache index increased from 38.0% (SD, 27.6; median, 36.3) during weeks 1 through 4 to 51.8% (SD, 33.0; median, 61.3) during weeks 5 through 8. As was the case with the overall headache index, this percentage improvement was maintained during weeks 9 through 12 (mean, 53.1%; SD, 36.3; median, 54.4). These shifts toward an increasing percentage of improvement in the peak headache index did reach statistical significance ($P<.0045$) primarily based on the increasing level of improvement during weeks 5 through 8 when compared to the first 4 weeks of treatment ($P<.005$).

The percentage improvement in overall headache frequency was less than the percentage improvement in the headache indexes, but did increase significantly over the three 4-week treatment periods, from a mean of 19.7% (SD, 19.6; median, 18.8) during weeks 1 through 4 to 31.7% (SD, 29.0; median, 37.5) during weeks 5 through 8, and 34.2% (SD, 33.0; median, 35.4) during weeks 9 through 12 ($P<.00045$). The increasing mean percentage of improvement in headache frequency between weeks 1 through 4 and weeks 5 through 8 also reached statistical significance ($P<.0039$).

The percentage of improvement in severe headache was more dramatic than for overall headache frequency, and very similar to what was seen in the peak headache index, climbing from a mean of 39.7% (SD, 34.7; median, 33.3) during weeks 1 through 4 to 61.1% (SD, 39.1; median, 77.5) during weeks 5 through 8 and 57.5% (SD, 36.2; median, 65.0) during weeks 9 through 12. The overall repeated-measures analysis of variance comparing the three 4-week treatment periods, however, did not reach statistical significance.

Table 2.—Percentage Improvement in Headache Diary Data

	Weeks 1 Through 4 (n = 38)	Weeks 5 Through 8 (n = 33)	Weeks 9 Through 12 (n = 30)
Frequency of headache*			
Median	18.8	37.5	35.4
Mean (SD)	19.7 (19.6)	31.7 (29.0)	34.2 (33.0)
Frequency of severe headache*			
Median	33.3	77.5	65.0
Mean (SD)	39.7 (34.7)	61.1 (39.1)	57.5 (36.2)
Overall headache index†			
Median	53.2	81.5	75.4
Mean (SD)	48.7 (33.7)	65.3 (34.6)	63.5 (35.9)
Peak headache index‡			
Median	36.3	61.3	54.4
Mean (SD)	38.0 (27.6)	51.8 (33.0)	53.1 (36.3)

*Total number of headache (and severe headache) days in 4-week interval.
†Overall headache index = (headache frequency × average intensity × duration)/28 days.
‡Peak headache index = (headache frequency × peak level of intensity)/28 days.

Analyses of overall deterioration in headache status after starting tizanidine were based on inspection of the overall headache index and peak headache index before negative percentages were converted to zero for the efficacy analyses. Two patients had increased headache on both measures during the first 4 weeks of treatment, but then showed significant improvement during the next 8 weeks, when the dose was titrated upward. For these two patients, the percentage improvement on the overall headache index was 67.4% and 93.4% during treatment weeks 9 through 12. Three patients showed some sustained overall deterioration in headache activity, but continued for the duration of the study. One patient showed deterioration during the first 4 weeks and dropped out of treatment due to lack of drug effectiveness, although the increase in headaches was not attributed to the medication. This patient also reported increased back pain, asthenia, abnormal dreaming, and developed an infection.

Treatment Responders.—The percentage of treatment responders (defined as at least a 50% improvement in headache compared to baseline) is summarized in Table 3. As shown, the percentage of responders varied dramatically, depending on the headache measure. For treatment weeks 9 through 12, percentage improvement ranged from a high of about 67% for the overall headache index as well as frequency of severe headaches to a low of 37% for overall headache frequency alone. For the overall headache index (arguably the best overall measure of headache activity), 50% of the patients met the 50% criterion of improvement during weeks 1 through 4, with 69.7% classified as responders during weeks 5 through 8, and 66.7% during weeks 9 through 12. Based on the peak headache index, 39.5% of the patients showed at least 50% improvement during weeks 1 through 4, increasing to 51.5% during weeks 5 through 8 and 50% during weeks 9 through 12.

When the classification of treatment responders was based on frequency measures alone, the most dramatic results were based on a high percentage of patients showing at least a 50% reduction in frequency of severe headaches: 39.5% during weeks 1 through

Table 3.—Treatment Responders*

	Weeks 1 Through 4 (n = 38)	Weeks 5 Through 8 (n = 33)	Weeks 9 Through 12 (n = 30)
Frequency of headache	3 (7.9)	9 (27.3)	11 (36.7)
Frequency of severe headache	15 (39.5)	21 (63.6)	20 (66.7)
Overall headache index†	19 (50)	23 (69.7)	20 (66.7)
Peak headache index‡	15 (39.5)	17 (51.5)	15 (50)

Values are number (percentage) of patients.
*Treatment responder defined as any patient with a reduction in headache frequency (total number of headache [or severe headache] days in 4-week interval) or headache index of at least 50% comparing the baseline period (week −4 through week −1) with a given treatment period.
†Overall headache index = (headache frequency × average intensity × duration)/28 days.
‡Peak headache index = (headache frequency × peak level of intensity)/28 days.

4, 63.67% during weeks 5 through 8, and 66.74% during weeks 9 through 12. However, when the identification of treatment responders was based on headache frequency alone (regardless of severity), the percentages were less dramatic: 7.9% with at least 50% improvement during weeks 1 to 4, and increasing to 27.3% during weeks 5 to 8 and to 36.7% during weeks 9 to 12.

Visual Analog Scales.—Significant overall improvement during the course of treatment based on the five administrations of the visual analog scales showed a significant improvement at $P<.00001$ for overall headache status, mood, sleep, and quality of life; with a trend toward improved ratings of sexual function ($P<.0075$). Post hoc analyses revealed that for each visual analog scale where significant improvement occurred, there was no significant change during the administrations of the scale at initial enrollment and the end of the baseline period. Significant improvement occurred at the end of the first 4 weeks of treatment, and then remained relatively stable during weeks 5 through 8 and weeks 9 through 12. These changes are illustrated in Figure 9.

Beck Depression Inventory-II.—There was a significant reduction in Beck Depression Inventory-II scores at the time of initial enrollment from a mean of 10.1 (SD, 8.5, median, 9.0) to a mean of 5.1 (SD, 6.1; median, 3.0) at the conclusion of the 12 weeks of treatment ($P<.00073$).

COMMENTS

Tizanidine was associated with significant improvement on all measures, with the headache indexes showing most improvement. Although the overall headache index is based not only on headache frequency (total headache days in the 4-week interval) but also includes measures of average intensity and duration, it could perhaps be argued that it is vulnerable to modification by changes in the patient's use of abortive/analgesic medication. However, patients actually decreased their abortive/analgesic use overall, and continued to use the same abortive/analgesic drugs that were used during baseline. They received no coaching on abortive/analgesic use. The headache index has, in fact, been used as a primary endpoint in double-blind, placebo-controlled studies of chronic tension-type head-

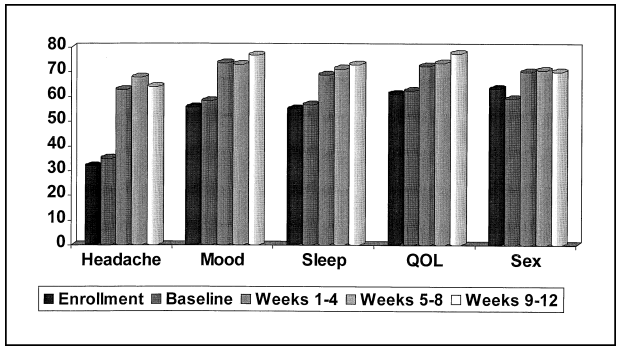

Fig 9.—Visual analog scales (0 = extremely bad, 100 = extremely good, mean rating). QOL indicates quality of life.

ache prophylaxis, and remains the best overall measure of headache activity.[23,24]

The study results raise the question of whether the overall headache improvement was primarily due to changes in background chronic tension-type headache, with little impact on migraine. Although patients were not asked to distinguish between migraine, migrainous, and tension-type headache in their diaries, the results showed the highest levels of improvement on the most severe headaches (eg, peak level of headache severity, frequency of severe headaches). Also, a post hoc analysis of improvement rates for the 33 patients who unequivocally met IHS criteria for migraine versus the 6 patients with less clearly defined migraine (only 1 of whom had pure chronic tension-type headache) found that those with migraine were more likely to be treatment responders: 72% versus 40% on the overall headache index during weeks 9 through 12, and 40% versus 20% on frequency alone. While these percentages favor patients with migraine, they do not reach statistical significance due to the small number of patients with nonmigraine headache.

On most measures, there was evidence of significant improvement during weeks 5 through 8 beyond what was achieved during weeks 1 through 4. Two patients whose headaches deteriorated during the first 4 weeks of treatment actually showed very significant levels of improvement on the overall headache index during treatment weeks 9 through 12 (67% and 93%). These results argue for the maintenance of scheduled tizanidine for at least 8 weeks (if tolerated) before judging treatment effectiveness. Although this study is obviously subject to all the limitations of a preliminary open-label study, the continuing improvement in treatment weeks 5 through 8 suggests that the results are not solely due to an initial placebo effect.

In summary, these results provide preliminary support for the efficacy of tizanidine as a novel prophylactic agent for the treatment of chronic daily headache with migraine or migrainous features, and are consistent with other recently published data.[11] Tizanidine was safe and generally well-tolerated, with an adverse event profile similar to what has been previously reported in other studies.[1,14] Tizanidine was actually associated with a trend toward improved sexual function (assessed by visual analog scale). The results strongly underscore the value of pursuing double-blind, randomized, placebo-controlled research on tizanidine as a prophylactic treatment for this difficult pain problem.

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