Research Submissions

Chronic Daily Headache Prophylaxis With Tizanidine: A Double-Blind, Placebo-Controlled, Multicenter Outcome Study

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Objective.—To assess the efficacy of tizanidine hydrochloride versus placebo as adjunctive prophylactic therapy for chronic daily headache (chronic migraine, migrainous headache, or tension-type headache).

Background.—Tizanidine is an α_2-adrenergic agonist that inhibits the release of norepinephrine at both the spinal cord and brain, with antinociceptive effects that are independent of the endogenous opioid system. Previous open-label studies have suggested the drug may be effective for treatment of chronic daily headache.

Methods.—Two hundred patients completed a 4-week, single-blind, placebo baseline period, with 134 fulfilling selection criteria and then randomized to tizanidine or placebo. Ninety-two patients completed at least 8 weeks of treatment (tizanidine, n = 45; placebo, n = 47), and 85 patients completed 12 weeks of treatment (tizanidine, n = 44; placebo, n = 41). Most patients (77%) met the diagnostic criteria for migraine of the International Headache Society; 23% had either chronic migrainous headache or chronic tension-type headache. Tizanidine was slowly titrated over 4 weeks to 24 mg or the maximum dose tolerated (mean, 18 mg; SD, 6.4; median, 20.0; range, 2 to 24), divided equally over three dose intervals per day. Overall headache index ([headache days × average intensity × duration in hours]/28 days) was the primary end point.

Results.—Tizanidine was shown to be superior to placebo in reducing the overall headache index ($P = .0025$), as well as mean headache days per week ($P = .0193$), severe headache days per week ($P = .0211$), average headache intensity ($P = .0108$), peak headache intensity ($P = .0020$), and mean headache duration ($P = .0127$). The mean percentage improvement during the last 4 weeks of treatment with tizanidine versus placebo was 54% versus 19% for the headache index ($P = .0144$), 55% versus 21% for severe headache days ($P = .0331$), 35% versus 19% for headache duration ($P = .0142$), 35% versus 20% for peak headache intensity ($P = .0106$), 33% versus 20% for average headache intensity ($P = .0281$), and 30% versus 22% for total headache days ($P = .0593$). Patients receiving tizanidine also scored higher ratings of overall headache improvement on a visual analog scale ($P = .0069$). There was no statistically significant difference in outcome for patients with chronic migraine versus those with only migrainous or tension-type headache. Adverse effects reported by more than 10% of the patients included somnolence (47%), dizziness (24%), dry mouth (23%), and asthenia (19%). Dropouts due to adverse events did not differ significantly between tizanidine and placebo.

Conclusions.—The results support tizanidine as an effective prophylactic adjunct for chronic daily headache, including migraine, migrainous headache, and tension-type headache. These results also suggest the possible importance of an α_2-adrenergic mechanism underlying the pathophysiology of this spectrum of headache disorders.

Key words: double-blind study, chronic daily headache, chronic migraine, chronic tension-type headache, prophylaxis, placebo-controlled, tizanidine

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Abbreviations: CDH chronic daily headache, CTTH chronic tension-type headache

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Chronic daily headache (CDH) has been defined as the persistent experience of head pain for at least 4 hours' duration for more than 15 days per month. Chronic daily headache is not currently included as a discrete formal diagnosis within the International Headache Society (IHS) classification system, although it does subsume several IHS diagnoses: very frequent migraine (chronic migraine), migrainous headache, chronic tension-type headache (CTTH), and hemicrania continua.[1] Recent, large-scale, population-based surveys have found the 6-month to 1-year prevalence of CDH to be about 4% to 5% (range, 3.9% to 4.7%).[2-4] Only about 37% of patients with CDH (1.5% of the general population) report headache every day.[2] Individuals with persistent and severe CDH (primarily those with chronic daily migraine) are the headache sufferers most likely to seek treatment at specialized headache centers, and have a lower quality of life than those with episodic migraine.[5-11]

To date, most treatment recommendations for CDH (chronic migraine) are based on open-label studies, retrospective case reviews, anecdotal observations, and generalization from the literature pertaining to episodic migraine and CTTH.[12,13] There are few placebo-controlled, double-blind treatment studies involving CDH. Patients with chronic migraine often are difficult to manage. There is frequently a need to reduce their overuse (ie, more than 2 to 3 days per week) of analgesics and abortive agents that otherwise may perpetuate persistent headache and block any positive response to prophylactic therapy.[14,15] Adjunctive behavioral therapy is often needed, as such improvement can sustain any improvement that follows initial detoxification and lead to better outcomes than those achieved with prophylactic medication alone.[6,16-18] Patients with severe forms of CDH who seek treatment at comprehensive headache centers are more likely to achieve reductions in the frequency of severe and incapacitating headache than in the overall frequency of headache.[7]

Tizanidine hydrochloride is an α_2-adrenergic agonist that has shown promise in the prophylaxis of CDH. Tizanidine inhibits the release and influence of norepinephrine in both the brain stem (eg, locus coeruleus) and spinal cord.[19] It acts as a central muscle relaxant but also has an antinociceptive effect that in animal studies has been demonstrated at doses below those required to produce muscle relaxation.[20] The antinociceptive effect does not involve the endogenous opioid system and appears to be centrally mediated by α_2-adrenoreceptors with little, if any, interaction with serotonin, dopamine, or γ-aminobutyric acid (GABA) receptors.[21,22] Double-blind, placebo-controlled outcome studies have shown tizanidine to produce significant reductions in low back pain.[14,15,23,24]

Standard formulation, commercially available tizanidine tablets have a half-life of approximately 2.5 hours.[25] The drug is completely absorbed after oral administration, and has linear pharmacokinetics at doses between 1 and 20 mg. Metabolites have half-lives between 20 and 40 hours but are not known to be active. Pharmacological studies in animals show similarities between tizanidine and the α_2-adrenergic agonist, clonidine, but with only 1/10 to 1/50 of the potency of clonidine in reducing blood pressure.[25]

A double-blind, placebo-controlled, randomized study demonstrated a significant clinical effect for tizanidine (in doses up to 6 mg three times per day) for CTTH, but a more recent double-blind study of an experimental (not commercially available) modified-release formulation, in doses comparable to 2 mg of the standard formulation three times per day, showed no beneficial effect.[26,27] An open-label study found that patients with tension-type headache (TTH) who had higher plasma levels of methoxy-hydroxy-phenylglycol (MHPG) (a product of cerebral norepinephrine metabolism) had the best headache response.[28] Since a primary effect of tizanidine hydrochloride is inhibition of the release of norepinephrine, the significantly superior treatment response in those with a biochemical marker of increased noradrenergic activity suggests a drug-specific effect on what may be an impor-

tant aspect of that headache disorder's pathophysiology. Results were encouraging in a recent large-scale clinical study involving 222 patients with either CTTH or CDH with coexistent migraine who were treated with tizanidine.[29] Doses used in this study were higher than those in previous studies; subjects titrated upward from 1 mg orally before bedtime to a maximum of 8 to 12 mg prior to sleep, plus 1 to 3 mg in the morning, at noon, and at supper.

An open-label study of tizanidine for CDH by Saper et al yielded similarly promising results.[30] Thirty-nine patients with more than 15 headache days per month (33 with migraine, 5 with migrainous headache, and 1 with CTTH) completed a 4-week baseline, with 31 subsequently completing the planned 12 weeks of treatment with tizanidine. Dosing was titrated from 2 mg at bedtime to a median daily dose of 14 mg divided over three doses per day (mean daily dose, 13.5 mg; SD, 4.3; range, 4 to 20) by treatment week 4. Overall headache frequency declined from 22.8 to 15.8 days per month ($P<.00001$), with frequency of severe headaches dropping from 7.5 to 3.5 days per month ($P<.000035$). Average headache intensity dropped from 1.8 to 1.1 (on a 1 to 5 scale), peak intensity declined from 2.4 to 1.4, and mean duration was reduced from 7.0 to 4.0 hours per headache (all at $P<.00001$).

For the group as a whole, the overall headache index (headache frequency × average intensity × duration) declined significantly through week 12 compared to baseline ($P<.00000002$). There was a corresponding and sequential increase in mean percentage improvement, from 49% during weeks 1 through 4 (drug titration phase), to 65% for weeks 5 through 8, and 64% for weeks 9 through 12 ($P<.0182$). By this measure, 50% of the patients met the 50% criterion of improvement during weeks 1 through 4, with 70% classified as responders during weeks 5 through 8 and 67% during weeks 9 through 12. 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 ($P<.00073$).

In this article, we present the results from a randomized, double-blind, placebo-controlled, multicenter (12 site) outcome study of tizanidine hydrochloride as an adjunctive prophylactic agent for CDH.

METHODS

Primary Objective and End Point.—The primary objective was to assess the efficacy of tizanidine hydrochloride for prophylaxis of CDH by evaluating changes in headache diary data. The overall headache index served as the primary end point and was calculated as the sum of the products of the number of headache days, average intensity, and duration for each headache during each 4-week interval (baseline, treatment weeks 1 through 4, weeks 5 through 8, weeks 9 through 12); divided by 28 days, as expressed in the formula: headache index = Σ(headache days × average intensity × duration in hours)/28 days.

Other Objectives and Outcome Measures.—Secondary end points were derived from changes recorded in headache diaries and included total headache days, severe headache days, severity (average intensity, peak intensity), and headache duration. Patients recorded peak and average levels of headache severity each day using a 6-point scale (0 to 5), as follows: 0 = no headache; 1 = mild headache, easily ignored; 2 = mild plus, bothersome discomfort; 3 = moderate, painful; 4 = moderate plus, very painful; 5 = severe, intensely painful. Headache duration was recorded as the number of hours of headache each day.

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 any analgesic/abortive medication used that day.

The patient's perception of overall headache status was assessed with a visual analog scale: a 100-mm line anchored at the left with the label "extremely bad" (0) and at the right with "extremely good" (10).

Data from the Migraine Disability Assessment (MIDAS) questionnaire also served as tertiary end points.[31] The questionnaire is a retrospective measure of the patient's report of days missed at work or school; days where work/school productivity was reduced by at least 50%; days with no household work completed; days when productivity in household work was reduced by at least 50%; and days with

missed family, social, or leisure activities. It also provides a retrospective estimate of days in the last 3 months that the patient had a headache, as well as a rating of how painful the headaches had been on average.

Safety and Tolerability.—The presence, significance, and severity of adverse events were assessed via the patient diaries, direct interview of patients, and changes in laboratory measures.

Inclusion Criteria.—Eligible participants included men or women between the ages of 18 and 65 who reported at least 15 days of headache per month for at least 3 months prior to entry. Specific headache types could include migraine, migrainous headache, and TTH as per IHS criteria.[1]

Exclusion Criteria.—Patients with prominent neurologic 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 level higher than 2 mg/dL), impaired liver function (serum glutamic-oxaloacetic transaminase [SGOT] or serum glutamate pyruvate transaminase [SGPT] higher than twice the upper normal limit), or severe, uncontrolled systemic hypertension (systolic blood pressure higher than 180 mm Hg, diastolic higher than 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 also were excluded. Patients with severe depression (Beck Depression Inventory-II score higher than 25) were excluded from the study.

Medication-related exclusion criteria included: previous failed treatment with three or more preventative medications given in adequate doses; use of symptomatic 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; at the discretion of the investigator, very limited use of promethazine or hydroxyzine was allowed for control of nausea. Women who were pregnant or breast-feeding, and sexually active women of childbearing potential who were not using medically accepted means of contraception also were excluded.

Concomitant Medication.—Patients were required to continue other permissible (ie, those with no known α_2-adrenergic impact) concurrent preventative/prophylactic medications at a stable dose between the screening and baseline visits, as well as throughout the study. Permissible symptomatic medications included simple analgesics (ie, aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs) and "migraine-specific" abortive agents (ie, ergots, isomethep- tene, triptans). Once enrolled, patients were not to add any new prophylactic or abortive medications, or alter doses.

Design.—We used a double-blind, placebo-controlled research design with a 4-week single-blind period of placebo treatment followed by 12 weeks of scheduled treatment (three times a day) with tizanidine versus placebo. Patients meeting entry criteria underwent screening evaluations, provided written informed consent, and received instructions to complete a daily headache diary for 1 month. All patients were started on placebo medication at the beginning of this baseline period.

After completion of the 1-month baseline period, patients returned for further evaluation and treatment randomization. Patients who continued to meet inclusion criteria (including headache diaries with at least 15 days of recorded headache activity over the baseline period) were given instructions to begin titration of the study medication the next day. Patients returned at weeks 4, 8, and 12 for review of completed diaries, assessment of adverse events, recording of vital signs, assessment of concomitant medication, pill counts, and provision of study medication sufficient for the next 4-week dosing period. Telephone contacts to discuss headache status, adverse events, diary compliance, drug management, and concomitant medications were scheduled at 2-week intervals between each visit.

Table 1.—Disposition of Safety Evaluable Population*

	Placebo Group (n = 63)	Tizanidine Group (n = 71)	Total (n = 134)	P†
Completed study	44 (69.8)	48 (67.6)	92 (68.7)	NS
Withdrew from study	19 (30.2)	23 (32.4)	42 (31.3)	NS
Reason for withdrawal				
Insufficient therapeutic effect	3 (4.8)	4 (5.6)	7 (5.2)	
Adverse event other than death	4 (6.3)	9 (12.7)	13 (9.7)	
Selection criteria/study compliance	5 (7.9)	1 (1.4)	6 (4.5)	
Lost to follow-up	1 (1.6)	0 (0.0)	1 (0.7)	
Patient request	4 (6.3)	5 (7.0)	9 (6.7)	
Patient died	0 (0.0)	0 (0.0)	0 (0.0)	
Other	2 (3.2)	4 (5.6)	6 (4.5)	

*Values are number (percentage)
†*P* values from *t* test for continuous variables and Cox-Mantel-Haenszel test for discrete variables.

Screening laboratory tests were performed at the first screening visit with repeat pregnancy testing at the end of the baseline period and prior to starting treatment. Follow-up laboratory tests were completed at weeks 4 and 12. Patients completed the visual analog scales at the end of the baseline period and then at weeks 4, 8, and 12. The MIDAS questionnaire was completed at initial enrollment and at the end of week 12 of treatment.

Medication and Placebo Protocol.—During the single-blind placebo baseline period, all patients received placebo tablets identical in appearance to 4 mg tizanidine. Titration began with one half of a tablet ("2 mg") at bedtime, and was gradually titrated at 3-day intervals to a total of two tablets three times a day (six tablets per day). Following randomization, the actual tizanidine or placebo dose was slowly titrated again, starting with one half of a 4-mg tablet (2 mg) at bedtime and titrating upward to the maximum tolerated dose or a maximum daily dose of 24 mg (six tablets), divided equally over three dose intervals per day.

RESULTS

Disposition of Patients.—A total of 200 patients were enrolled in the single-blind placebo phase of the study. Of this group, 136 completed the baseline period, met inclusion/exclusion criteria, and were randomized under double-blind conditions (64 to placebo, 72 to tizanidine). Two of these patients (1 placebo, 1 tizanidine) failed to initiate drug exposure, leaving 134 randomized patients who were evaluable. Of these 134 patients, 92 (45 tizanidine, 47 placebo) met the criterion for efficacy analysis (ie, at least 8 weeks of double-blind therapy without major protocol violations), and 85 (44 tizanidine, 41 placebo) completed all 12 weeks of treatment. The proportion of patients withdrawn from the study did not differ significantly for placebo-treated patients (19 [30.2%] of 63) versus those treated with tizanidine (23 [32.4%] of 71). These data are displayed in Table 1.

Table 2.—Headache History*

	Placebo Group (n = 47)	Tizanidine Group (n = 45)	P‡
History of chronic headache†			NS
3-6 months	1 (2.1)	2 (4.4)	
6-12 months	4 (8.5)	3 (6.7)	
1-2 years	9 (19.1)	7 (15.6)	
3-5 years	6 (12.8)	7 (15.6)	
>5 years	27 (57.4)	26 (57.8)	
Frequency			NS
4-5 days/week	26 (55.3)	24 (53.3)	
6-7 days/week	21 (44.7)	21 (46.7)	

*Values are number (percentage).
†Chronic headache defined as present more than 15 days per month.
‡*P* value using *t* test for continuous variables and Cox-Mantel-Haenszel test for discrete variables.

Table 3.—Migraine Features*

Feature	Placebo Group (n = 47)	Tizanidine Group (n = 45)	*P*†
Diagnosis (IHS)			NS
Migraine	37 (78.7)	34 (75.6)	
Migraine or CTTH	10 (22.3)	11 (24.4)	
Typical intensity			NS
Mild	2 (4.3)	4 (8.9)	
Moderate	34 (72.3)	33 (73.3)	
Severe	11 (23.4)	8 (17.8)	
Quality			
Throbbing	37 (78.7)	35 (77.8)	NS
Aggravated by activity	35 (74.5)	34 (75.6)	NS
Typical location			
Unilateral	21 (44.1)	23 (51.5)	NS
Associated symptoms			
Photophobia	39 (83.0)	34 (75.6)	NS
Phonophobia	33 (70.2)	30 (66.7)	NS
Nausea	34 (72.3)	32 (71.1)	NS

*Values are number (percentage). IHS indicates International Headache Society; CTTH, chronic tension-type headache.
†*P* value using *t* test for continuous variables and Cox-Mantel-Haenszel test for discrete variables.

Table 4.—Headache Impact*

Impact	Placebo Group (n = 47)	Tizanidine Group (n = 45)	*P*†
Overall			NS
None	6 (12.8)	2 (4.4)	
Mild	16 (34.0)	14 (31.1)	
Moderate	19 (40.4)	26 (57.8)	
Severe	6 (12.8)	3 (6.7)	
Social			NS
None	2 (4.3)	4 (8.9)	
Mild	19 (40.4)	18 (40.0)	
Moderate	20 (42.6)	19 (42.2)	
Severe	6 (12.8)	4 (8.9)	
Work			NS
None	1 (2.1)	4 (8.9)	
Mild	21 (44.7)	16 (35.6)	
Moderate	21 (44.7)	19 (42.2)	
Severe	3 (6.4)	4 (8.9)	

*Values are number (percentage).
†*P* value using *t* test for continuous variables and Cox-Mantel-Haenszel test for discrete variables.

Modifications in dosing were based on tolerability. For those patients included in the efficacy analysis (ie, those completing at least 8 weeks of treatment under the double-blind conditions), tizanidine exposure remained relatively stable. For weeks 5 through 8, the mean total daily tizanidine dose was 18.0 mg (SD, 6.0; median, 20.0; range, 2 to 24). For weeks 9 through 12, the mean total daily dose was 18.4 mg (SD, 6.4; median, 20.0; range, 2 to 24).

Age, gender, and race/ethnicity did not differ between the efficacy evaluable populations of the two treatment groups. In the randomized sample, 79% were women and 89% were white. Mean age was 40.3 years (SD, 11.7; median, 41.45; range, 18.7 to 64.6).

As shown in Tables 2, 3, and 4, headache characteristics also did not differ significantly between the two groups. For the efficacy evaluable population (those completing at least 8 weeks of treatment), 70% of the placebo-treated subjects and 73% of those receiving tizanidine reported at least a 3-year history of CDH (ie, more than 15 headache days per month). Headaches that did not meet IHS criteria for migraine were classified as either migrainous or tension-type. About three fourths of the patients in each treatment group had IHS-diagnosed migraine, and about one fourth had either migrainous headaches or CTTH. More than 90% of the patients in both the placebo and tizanidine groups rated their typical headache

Table 5.—Treatment-Emergent Adverse Events*

	Placebo Group (n = 63)	Tizanidine Group (n = 71)	*P*†
Adverse event			
Somnolence	3 (4.8)	33 (46.5)	<.0001
Dizziness	4 (6.3)	17 (23.9)	.0077
Dry mouth	1 (1.6)	16 (22.5)	.0002
Asthenia	2 (3.2)	14 (19.7)	.0031
Rated intensity of adverse events			.0717
None	17 (27.0)	8 (11.3)	
Mild	14 (22.2)	13 (18.3)	
Moderate	24 (38.1)	35 (49.3)	
Severe	8 (12.7)	15 (21.1)	

*Values are number (percentage).
†*P* value using *t* test for continuous variables and Cox-Mantel-Haenszel test for discrete variables.

Table 6.—Overall Headache Index

	Placebo Group		Tizanidine Group		
	Actual	Change From Baseline	Actual	Change From Baseline	*P**
Week −4 to week −1 (baseline)					
No. of patients	47		45		
Mean (SD)	2.6 (3.4)		2.6 (2.8)		
Median	1.1		1.8		
Minimum-maximum	0.2-17.7		0.1-11.9		
Weeks 1-4					
No. of patients	47	47	45	45	
Mean (SD)	2.6 (3.9)	0.0 (1.7)	1.5 (2.0)	−1.1 (1.4)	
Median	1.0	−0.2	0.9	−0.7	
Minimum-maximum	0.0-18.2	−4.0-6.3	0.0-9.1	−5.4-0.7	
Weeks 5-8					
No. of patients	47	47	45	45	.0117†
Mean (SD)	2.2 (4.1)	−0.4 (1.8)	1.2 (1.9)	−1.4 (1.7)	
Median	0.7	−0.4	0.4	−1.0	
Minimum-maximum	0.0-21.9	−4.1-5.2	0.0-7.7	−8.3-1.0	
Weeks 9-12					
No. of patients	41	41	44	44	.0097‡
Mean (SD)	1.7 (3.2)	−0.5 (1.7)	1.2 (1.8)	−1.5 (1.6)	
Median	0.5	−0.3	0.4	−0.9	
Minimum-maximum	0.0-14.3	−3.3-5.8	0.0-6.6	−7.3-0.3	
Final visit (last 4 weeks of treatment)					
No. of patients	47	47	45	45	.0144§
Mean (SD)	2.1 (4.2)	−0.5 (1.8)	1.2 (1.8)	−1.5 (1.6)	
Median	0.5	−0.4	0.4	−0.9	
Minimum-maximum	0.0-21.9	−4.1-5.8	0.0-6.6	−7.3-0.3	
Repeated-measures ANOVA across follow-up visits					.0025‖

*P value using an ANCOVA model with main effects of treatment, site, and baseline.
†Change from baseline to week 5 through week 8.
‡Change from baseline to week 9 through week 12.
§Change from baseline to final visit.
‖P value using repeated-measures ANOVA with main effects of treatment and visit.

intensity as moderate to severe, and over half in each group rated headache impact as moderate to severe.

Safety and Tolerability.—Table 5 depicts the four adverse events (somnolence, dizziness, dry mouth, and asthenia) that occurred significantly more often with tizanidine than with placebo. Tizanidine-exposed patients tended to report more adverse events than placebo-treated patients and to rate those events as more severe ($P = .0717$). As shown in Table 1, dropouts due to adverse events did not differ significantly between the tizanidine (9 [12.7%] of 71) and placebo (4 [6.3%] of 63) groups. Dropouts generally reported multiple adverse events. Headache was a relatively rare adverse event that did not differ between tizanidine and placebo, reported by 4 (5.6%) of 71 of the tizanidine-treated patients (including 1 who dropped out of treatment) and 2 (3.2%) of 63 of the placebo-treated patients. Treatment-emergent moderate elevation of liver function tests occurred in 1 (1.4%) of the 71 patients exposed to tizanidine and in 1 (1.6%) of 63 patients who remained on placebo. Serious adverse events included a suicide attempt and unintended pregnancy in the placebo group and a breast carcinoma and vaginal hemorrhage in the tizanidine group, all events that were not thought to be related to treatment. There were no deaths.

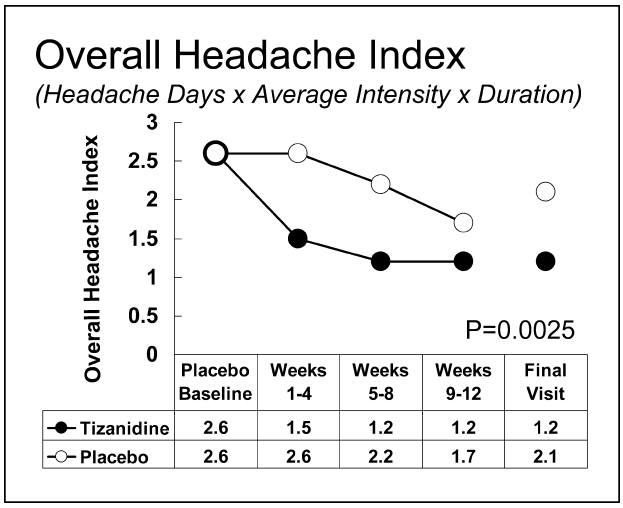


Fig 1.—Overall headache index.

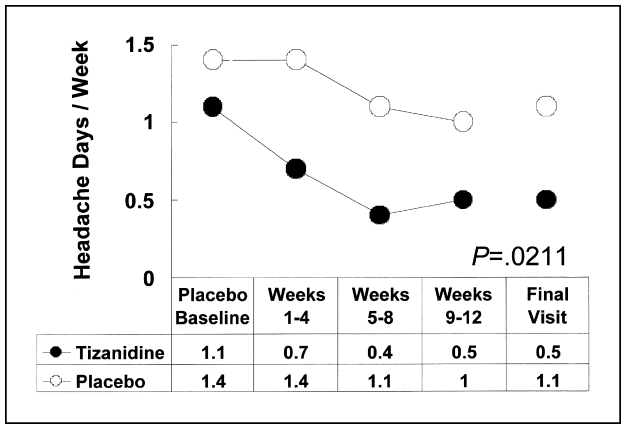


Fig 3.—Severe headache days per week.

Headache Index (Primary End Point).—Table 6 lists headache index data from patient diaries for the efficacy evaluable population of patients completing at least 8 weeks of treatment. Based on a repeated-measures analysis of variance (ANOVA) with main effects for treatment and visit, tizanidine was significantly more effective than placebo ($P = .0025$). The tizanidine-treated patients also exhibited a significant change in this variable when their single-blind baseline headache indices were compared with those from treatment weeks 5 through 8 ($P = .0117$) and weeks 9 through 12 ($P = .0097$), based on analyses of covariance (ANCOVA) with main effects of treatment, site, and baseline. As shown in Table 6, more placebo-treated patients (n = 6) than tizanidine-treated patients (n = 1) dropped out during treatment weeks 9 through 12. Comparison of the last 4 weeks of treatment (weeks 5 through 8 for dropouts, weeks 9 through 12 for completers) also revealed tizanidine to be superior to placebo ($P = .0144$). These results are also displayed graphically in Figure 1.

Other Headache Diary Variables.— Tizanidine emerged as more effective than placebo on all headache measures from the diary data, including mean headache days per week ($P = .0193$), severe headache days per week ($P = .0211$), average headache intensity ($P = .0108$), peak headache intensity ($P = .0020$), and mean headache duration ($P = .0127$), based on repeated-measures ANOVA with main effects of treatment and visit. These results are depicted in Figures 2

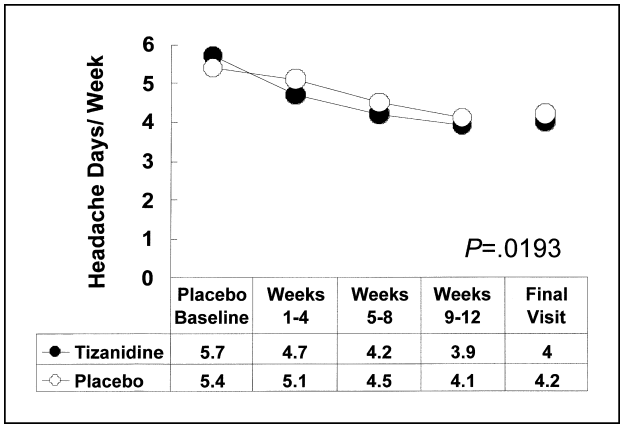


Fig 2.—Mean headache days per week.

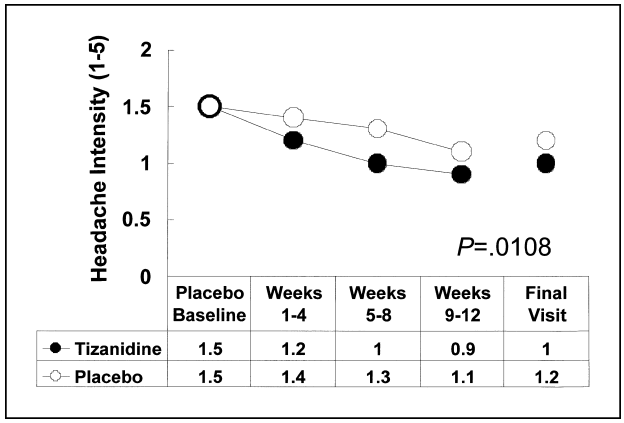
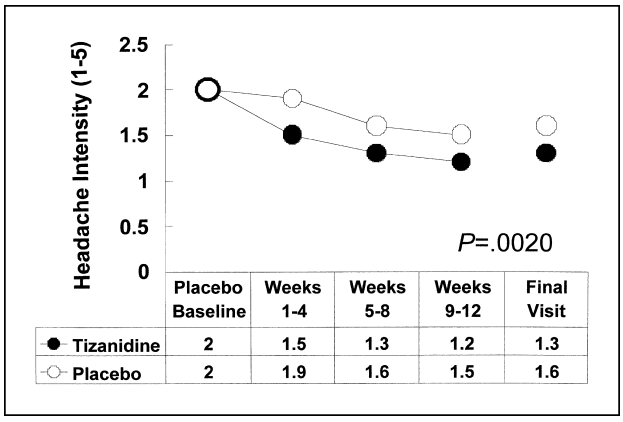
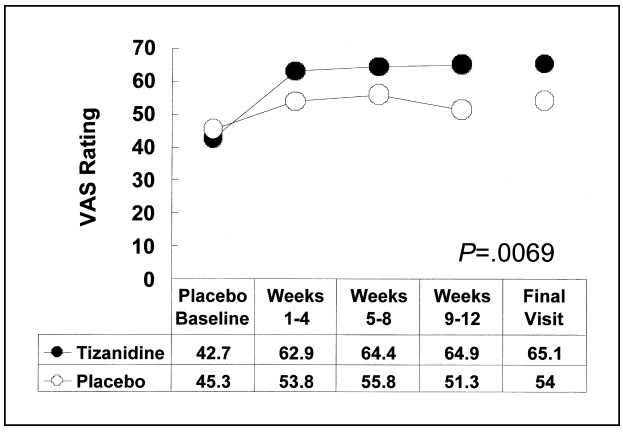


Fig 4.—Average headache intensity.



	Placebo Baseline	Weeks 1-4	Weeks 5-8	Weeks 9-12	Final Visit
Tizanidine	2	1.5	1.3	1.2	1.3
Placebo	2	1.9	1.6	1.5	1.6

Fig 5.—Peak headache intensity.

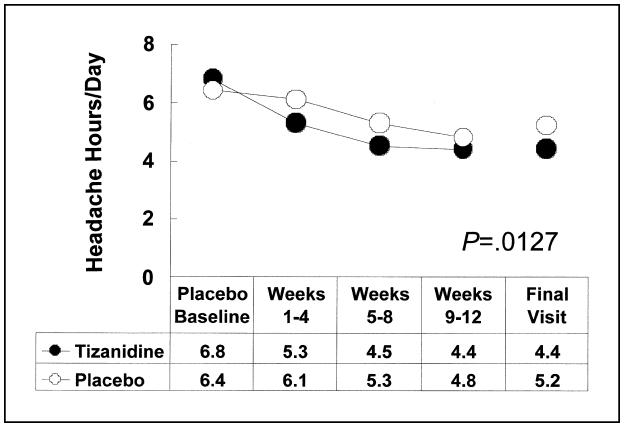


	Placebo Baseline	Weeks 1-4	Weeks 5-8	Weeks 9-12	Final Visit
Tizanidine	42.7	62.9	64.4	64.9	65.1
Placebo	45.3	53.8	55.8	51.3	54

Fig 7.—Visual analog scale (VAS) (0 to 100; 0 = extremely bad, 100 = extremely good).

through 6. The perceived percentage improvement at the final visit was 52% for tizanidine versus 19% for placebo, calculated by subtracting the single-blind baseline value from the final visit and dividing by the single-blind baseline value. As illustrated in Figure 7, tizanidine was also superior to placebo on the visual analog scale of perceived improvement ($P = .0069$, based on the repeated-measures ANOVA with main effects of treatment and visit).

Percentage Improvement in Headache Variables.— The mean percentage reduction in headache activity for each of the headache diary variables was computed by subtracting the final visit value from the single-blind baseline value and then dividing by the baseline value. These results are illustrated in Figure 8, with the probability value for the tizanidine-placebo comparison for the last 4 weeks of treatment compared to baseline, using an ANCOVA model with main effects of treatment, site, and baseline. As shown, the greatest improvement occurred in the overall headache index (54% tizanidine, 19% placebo; $P = .0144$) and days with severe headache (55% tizanidine, 21% placebo; $P = .0331$). In the tizanidine group, percentage improvement values for peak intensity (35%), average intensity (33%), and headache duration (35%) also were significantly greater than those in the placebo group, wherein values ranged from 19% to 20%. Although the overall ANOVA clearly showed tizanidine to be more effective than placebo in reducing total days with headache (ie, $P = .0193$ for the repeated-measures ANOVA with main effects for treatment condition and study period), the drug's superiority by this measure only approached significance when the final 4 weeks of treatment were compared with baseline (30% versus 22%, $P = .0593$).



	Placebo Baseline	Weeks 1-4	Weeks 5-8	Weeks 9-12	Final Visit
Tizanidine	6.8	5.3	4.5	4.4	4.4
Placebo	6.4	6.1	5.3	4.8	5.2

Fig 6.—Mean headache duration.

Migraine Versus Migrainous/Tension-type Headaches.—To assess whether there was differential improvement according to headache type (migraine versus migrainous headache or CTTH), we performed a post hoc analysis. As a relatively small number of patients did not meet IHS criteria for migraine, we combined the migrainous headaches and the tension-type headaches. There was no statistically significant difference in outcome for tizanidine-treated patients with migraine versus tizanidine-treated patients with CTTH or migrainous headaches.

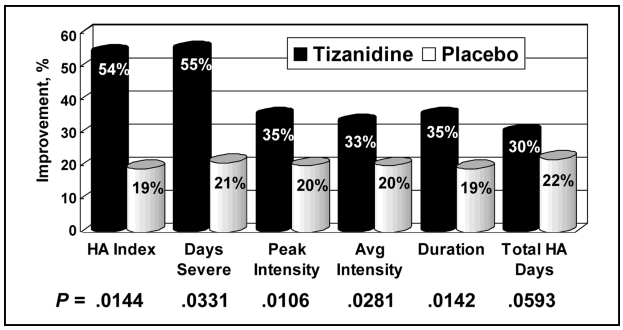


Fig 8.—Percentage reduction in headache index last 4 weeks of treatment compared to single-blind placebo baseline.

Use of Analgesics/Abortive Agents.—On this measure, there was no significant difference between tizanidine and placebo. The mean number of days of analgesic/abortive use remained below 2 days per week from baseline through the final visit.

MIDAS Measures.—None of the MIDAS measures showed any differential effect for tizanidine versus placebo.

COMMENTS

Tizanidine was superior to placebo for the primary end point, headache index (a composite measure of headache frequency, average intensity, and duration), with a mean percentage improvement during the last 4 weeks of treatment of 54% (versus 19% for placebo). Tizanidine was also more effective than placebo on all individual diary measures of headache activity, and patients perceived tizanidine to be more effective than placebo on the visual analog scale by a similar margin of improvement: 52% (tizanidine) versus 19% (placebo) at the final visit.

These results are consistent with the improvement rates from tizanidine observed in our previous open-label study, wherein subjects experienced a mean percentage improvement of 67% in the headache index during weeks 9 through 12 of treatment compared to baseline.[30] The study reported here included a single-blind, placebo baseline period, and the most dramatic placebo responders (ie, those whose headaches dropped below the threshold frequency of 15 days per month) were eliminated prior to randomization. The 13% difference in outcome between our open-label study results (67% improvement) versus those reported here (54%) may result from the elimination of those placebo responders.

The use of the headache index as the primary end point has historical precedence and a sound rationale but nonetheless remains somewhat controversial. The evidence-based guidelines endorsed by the US Headache Consortium identify three goals for prophylaxis: (1) reduce attack frequency, severity, and duration; (2) improve responsiveness to treatment of acute attacks; and (3) improve function and reduce disability.[13,32,33] The headache index is a composite measure that incorporates the first two goals. Abortive/analgesic/rescue medication was limited in this study, with patients allowed only to use the same abortive/analgesic/rescue protocols during both baseline and treatment phases. Since there were no significant differences between the tizanidine and placebo groups in regards to use of symptomatic medications at baseline, and only a modest reduction in such use following initiation of treatment for both tizanidine and placebo, the differential reduction in both intensity and duration of headaches for tizanidine versus placebo implies that patients experienced an increase in the effectiveness of analgesics and abortive agents after tizanidine was added. Most of the studies cited in support of evidence-based treatment by the Consortium have relied on a headache index, combining frequency, severity, and duration.

In contrast, the IHS's "Guidelines for Controlled Trials of Drugs in Migraine" specifically recommends frequency of headache as the primary end point for assessing the efficacy of prophylaxis, at least in controlled trials, since intensity and duration are compounded by acute and rescue therapies.[34] Even so, the IHS guidelines concede that "Conceivably the headache indices . . . better reflect the total suffering of patients."[34(p778)] In this study, the percentage improvement at the final visit for the headache index and the visual analog scale of perceived improvement were almost identical for both tizanidine and placebo. The headache index has been used as a primary end point in published double-blind, placebo-controlled studies of CTTH conducted by respected members of the IHS.[35,36] Also of note is that the IHS guidelines were developed for application to episodic migraine, not CDH.

Recent reports describing peripheral and central sensitization in migraine and temporal summation of

pain in CDH raises the possibility that some prophylactic agents may exert their effect by influencing the sensitization of excitatory circuits, thereby reducing the intensity and duration of pain and, perhaps, increasing the efficacy of abortive agents.[37-39] Although tizanidine is a centrally acting muscle relaxant, it has significant impact on noradrenergic α_2-receptors in the brain stem (locus ceruleus) that reside in the general vicinity of the brain stem generator or modulator currently believed to play a key role in migraine pathophysiology.[40-42] The results reported here do not seem to support a simple muscle relaxation effect. Tizanidine was more successful in preventing severe headaches (most likely those with more migraine features) than in reducing the overall frequency of headache. Conversely, there was no difference in response for patients with IHS-diagnosed migraine compared to those with migrainous or chronic tension-type features, a finding consistent with results from open-label clinical trials.[29,30] These findings may possibly suggest that an α_2-adrenergic mechanism contributes to the pathophysiology of the entire spectrum of head pain that runs from TTH through migrainous headache and to migraine.

Tizanidine was generally well tolerated by our patients. The majority of adverse events were rated as mild to moderate, and dropouts due to adverse events did not differ significantly between the tizanidine and placebo groups. While on tizanidine, somnolence was reported by almost half of our patients, dizziness and dry mouth by about 1 in 4, and asthenia by 1 in 5. The package insert for tizanidine reports elevation of liver enzymes to more than three times normal in about 5% of treated patients and recommends monitoring liver tests at baseline, 1, 3, and 6 months after starting treatment. Only 1 (1.4%) of our 71 patients exposed to tizanidine experienced elevation of liver enzymes, and levels returned to normal after drug discontinuation.

In summary, these results provide support for the use of tizanidine as an adjunctive prophylactic agent for the treatment of CDH, including CDH with migraine, migrainous, or chronic tension-type features. Patients with clinically severe CDH often require "rational polypharmacy." Tizanidine's unique mechanism of action and lack of involvement with the P-450 system render it useful in that circumstance. Its efficacy as a monotherapeutic agent remains to be determined.

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