Modified-Release Formulation of Tizanidine in Chronic Tension-type Headache

K. Murros, MD; M. Kataja, PhD; C. Hedman, MD; H. Havanka, MD; E. Säkö, MD; M. Färkkilä, MD; J. Peltola, MD; T. Keränen, MD, for the Finnish Sirdalud Study Group

The efficacy of the modified-release formulation of tizanidine (Sirdalud) was compared with placebo in a randomized, double-blind, parallel-group study of 138 women and 47 men, aged 18 to 79 years, with a history of chronic tension-type headache (IHS categories 2.2 and 2.3). The treatment period was 6 weeks preceded by a 2-week prerandomization period. The patients were randomly assigned to receive 6-mg Sirdalud, 12-mg Sirdalud MR, or placebo. The study medication was taken once per day, orally in the evening. Efficacy was measured by visual analog scale, the number of headache-free days, the daily duration of headache, and the use of paracetamol. The primary end point was the severity of daily headache derived from visual analog scale scores covering the last 2 treatment weeks. One hundred sixty patients (56 in the 6-mg group, 49 in the 12-mg group, and 55 in the placebo group) completed the study. The severity of the headache decreased similarly in the treatment groups and the placebo group. The visual analog scale values decreased from the prerandomization values by 53% in the 6-mg group, 48% in the 12-mg group, and 52% in the placebo group. The modified-release formulation of tizanidine in doses up to 12 mg taken in the evening is not superior to placebo in the treatment of chronic tension-type headache. The placebo effect was unexpectedly strong in the present study, supporting the view that psychophysiological mechanisms are of considerable importance in sustaining chronic tension-type headache.

Key words: α_2-adrenergic agonist, chronic tension-type headache, tizanidine, Sirdalud

Abbreviations: CTTH chronic tension-type headache, VAS visual analog scale, MR modified-release

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Tizanidine hydrochloride is an imidazole derivative and acts as a central α_2-adrenergic agonist.[1] It has muscle relaxant[1-3] and antinociceptive properties[4] and has been successfully used in patients with musculoskeletal conditions of the neck.[5] Tizanidine hydrochloride may also be beneficial in patients with chronic tension-type headache (CTTH). In a randomized, double-blind, placebo-controlled, crossover study of 37 women with CTTH, Fogelholm and Murros[6] reported that the standard formulation of tizanidine (Sirdalud) was superior to placebo as assessed by the patients on a visual analog scale (VAS) and verbal rating scale, by the number of headache-free days, and by the amount of analgesics needed. The pathophysiologic explanation for this favorable effect is not known. Although CTTH is the most common form of headache, its basic pathophysiology is poorly understood. Individuals with CTTH usually have increased EMG activity in their pericranial muscles,[7] but the activity levels do not seem to correlate with the severity of the headache[7] or treatment results.[6] According to Shimomura et al[8] and Fogelholm and Murros,[6] a reduction of central adrenergic hyperactivity may partially explain the favorable effect of tizanidine in CTTH. Before tizanidine can be recommended for widespread use to

From the Jorvi Hospital, Espoo (Dr. Murros); National Public Health Institute (Dr. Kataja) and Helsinki University Hospital (Dr. Färkkilä), Helsinki; Lohja District Hospital (Dr. Hedman); Central Hospital, Länsi-Pohja (Dr. Havanka); Turku Headache Center (Dr. Säkö); and Tampere University Hospital (Drs. Peltola and Keränen), Finland. In addition to the authors, the Finnish Sirdalud Study Group included M. Ilmavirta, M. Nissilä, A. Salmivaara, and A. Rissanen.

Address all correspondence to Dr. Kari Murros, Jorvi Hospital, 02740 Espoo, Finland.

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treat CTTH, confirmatory studies are needed. The modified-release (MR) formulation of tizanidine may have advantages over the standard formulation as compliance and tolerability may be better with the MR formulation. In contrast to the standard formulation, the MR tablet does not have high plasma concentration peaks and maintains steady plasma concentrations over 24 hours.[1] A multicenter study was carried out in six centers in Finland to study the effect of tizanidine MR in CTTH.

PATIENTS AND METHODS

The study was a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Men and women, aged 18 or older, who fulfilled the International Headache Society criteria[9] for CTTH (category 2.2) were enrolled. In addition, patients who had had tension-type headache for at least 3 months and otherwise fulfilled the criteria of CTTH at the time of screening were eligible. Patients who had headache episodes for less than 15 but more than 7 days per month and fulfilled the criteria of CTTH (category 2.3) were also eligible. The following patients were excluded from the study: patients with migraine (more than 1 day per month); patients who had been treated with muscle relaxants, such as chlormezanone, or who had had physical treatment, including acupuncture, for CTTH within 2 weeks; patients who were current users of psychoactive medication, such as neuroleptics, anxiolytics, antidepressants, or neurostimulants, or of particularly toxic drugs, such as cytostatics; patients who were current users of α_2-agonists or who had a history of adverse events to these compounds (including patients who had not tolerated tizanidine MR earlier); patients who had a history of recent alcohol or drug abuse, mental dysfunction, or any factor limiting the ability to cooperate; patients who had clinically relevant pathological conditions of the gastrointestinal tract, liver, or kidneys; patients who had untreated hypotension or labile hypertension; patients who were women of childbearing potential without appropriate contraception or who were pregnant or lactating; and patients who had recently received any investigational drug. Because paracetamol was used as a first-line escape medication, patients with paracetamol intolerance were excluded. At the screening visit, a physical examination was performed that included a neurologic examination and palpation of the neck muscles.

At the baseline visit, those willing to participate and who were eligible for the study completed the Beck Depression Inventory (BDI) Short Form.[10] A headache diary was given to assess the severity and duration of headache on a daily basis (100-mm VAS, daily duration of headache in hours, use of paracetamol and other analgesics). Patients were randomized 2 weeks ($\pm$2 days) after the baseline visit. The treatment group assignment was computerized and conducted by Novartis Pharma AG (formerly, Sandoz Pharma AG). Patients who were not compliant (VAS information available for less than 70% of the days during the 2-week prerandomization phase) were not entered into the study. At the randomization visit, the patients assessed the impact of headache on their quality of life on a 5-point severity scale (global impression of severity scale [GISS]). The patients were randomly assigned to three groups to receive 6-mg tizanidine MR (25% of the patients), 12-mg tizanidine MR (25% of the patients), or placebo (50% of the patients). The study medication was taken orally once a day in the evening. During the first 2 weeks of treatment, all patients received 6-mg tizanidine MR or matching placebo. After 2 weeks of treatment, the daily dose was randomly and blindly increased to 12 mg in half of those receiving active drug. The doses were maintained for the following 4 weeks (ie, until the end of the study). Study medication started on the day of randomization. Follow-up visits took place 2, 4, and 6 weeks after the start of treatment. At the final evaluation (week 6), the headache diaries were collected, and the scores on a 7-point global impression of change scale (GICS) for quality of life were recorded.

The primary efficacy variable was the average severity of daily headache during the last 2 weeks of treatment. Two-way analysis of variance (ANOVA) was used to evaluate differences between group means for the efficacy variables (VAS, days free of headache, daily duration of headache, use of paracetamol). The mean differences between baseline and follow-up values within groups was determined by the paired *t* test. A *P* value of less than .05 was considered to be statistically significant.

RESULTS

There were 201 patients in the prerandomization phase. After exclusion of noncompliant patients, 185 patients (138 women and 47 men) were randomized. The mean age of the randomized patients was 44.0 years (range, 18 to 79 years), with a mean duration of headache of 99.3 months (Table 1).

Of the 185 patients, 160 completed the study. The mean 2-week VAS values of the completers based on daily median VAS values decreased significantly over time in all three groups (Table 2). When the VAS values were compared over time, no statistically significant differences between the groups were demonstrated. The change in VAS values from the pretreatment VAS values were comparable (Table 3). The proportion of headache-free days was also comparable (Table 4). During follow-up, the proportion of days free of headache increased by 28% in the 6-mg group, 18% in the 12-mg group, and 24% in the placebo group. Before treatment, the mean values of the daily duration of headache differed slightly between groups (Table 5). During treatment phase, the mean reduction of the mean duration of headache episodes did not differ statistically (ANOVA, $F_{2,467} = 1.602$; P = NS). Accordingly, the use of paracetamol as rescue medication did not differ between the treatment groups during the study (data not shown).

Neck palpation data was available for the screening visit and the last (6-week) visit for 153 completers.

Table 1.—Patient Data

	6 mg	12 mg	Placebo	Total
Ratio of women to men	49:15	44:16	45:16	138:47
IHS diagnosis 2.2*	47 (7)	49 (9)	41 (4)	137 (20)
IHS diagnosis 2.3*	17 (1)	11 (2)	20 (2)	48 (5)
Mean age, y	41.3	46.2	44.6	44.0
Mean TTH duration, mo	89.9	116.3	92.2	99.3
Mean prerandomization BDI score	3.8	4.9	4.6	4.4
Mean prerandomization GISS score	2.9	3.1	3.0	3.0

The numbers in parentheses indicate withdrawals. TTH indicates tension-type headache; BDI, Beck Depression Inventory; and GISS, global impression of severity scale.

Table 2.—Mean Visual Analog Scale Values*

Duration of treatment, wk	6 mg (n=56)	12 mg (n=49)	Placebo (n=55)
Prerandomization	21.9 (18.9)	21.7 (19.0)	23.2 (21.1)
1-2	16.2 (20.2)	14.9 (17.7)	16.9 (19.4)
3-4	10.7 (19.6)	15.3 (20.5)	12.2 (18.2)
5-6	10.4 (20.3)	11.3 (16.0)	11.1 (18.2)

*Values are expressed in millimeters (SD).
ANOVA between groups: $F_{2,632} = 0.211$; P = NS.

When controlled for the presence of pericranial tenderness (present in 132 completers) or typical CTTH (117 of all completers were in category 2.2), there were no statistically significant differences between the groups in the overall efficacy (VAS, days free of headache, daily duration of headache, paracetamol use) or in the 6-week GICS scores (ANOVA).

The medication was well tolerated. Twelve patients on active drug versus 2 on placebo tolerated the medication poorly or very poorly. Twenty-five were withdrawn from the study; 14 for adverse events and 11 for noncompliance, protocol violation, illness not related to study, or treatment failure. Tiredness and dry mouth were the most frequent adverse events. Twenty-one patients (17%) on active drug and 9 (15%) on placebo complained of tiredness. Twenty-seven patients (22%) on active drug and none on placebo complained of dry mouth.

COMMENTS

The MR formulation of tizanidine up to a dose of 12 mg taken once in the evening is not therapeutically

Table 3.—Change in Visual Analog Scale Values*

Duration of Treatment, wk	6 mg (n=56)	12 mg (n=49)	Placebo (n=55)
Prerandomization	0	0	0
1-2	−5.7 (14.1)	−6.8 (12.2)	−6.3 (19.9)
3-4	−11.2 (15.6)	−6.4 (16.2)	−11.0 (20.1)
5-6	−11.5 (17.0)	−10.4 (16.1)	−12.1 (20.6)

*Values are expressed in millimeters (SD).
ANOVA between groups: $F_{2,473} = 0.561$; P = NS.

Table 4.—Days Free of Headache*

Duration of Treatment, wk	6 mg (n=56)	12 mg (n=49)	Placebo (n=55)
Prerandomization	28.4 (23.8)	27.6 (24.6)	27.0 (25.0)
1-2	39.0 (28.3)	38.6 (29.0)	37.1 (29.3)
3-4	53.0 (32.2)	40.6 (30.3)	42.7 (31.6)
5-6	56.5 (32.3)	45.8 (34.5)	50.9 (31.8)

*Values are percentages of all days (SD).
ANOVA between groups: $F_{2,632} = 2.551$, P = NS.

Table 5.—Daily Mean (SD) Duration of Headache*

Duration of Treatment, wk	6 mg (n=56)	12 mg (n=49)	Placebo (n=55)
Prerandomization	4.00 (3.05)	5.02 (3.63)	5.51 (5.18)
1-2	3.20 (3.15)	4.01 (4.15)	4.40 (4.21)
3-4	2.73 (3.23)	3.61 (3.03)	3.65 (4.07)
5-6	2.81 (3.87)	3.10 (2.84)	3.33 (3.93)

*Values are expressed in hours.
ANOVA between groups: $F_{2,625} = 4.448$; $P < .05$.

effective in the treatment of CTTH. This finding differs from those of earlier studies using the standard formulation of tizanidine. In open-label trials, headache improvement has been demonstrated in 70% to 90% of the patients using the standard formulation 1 mg three times daily.[8,11,12] However, a placebo effect may explain the favorable results. In the present study, the placebo effect was unexpectedly high. As measured by the VAS, a pain reduction of about 50% was observed in the placebo group. The number of headache-free days almost doubled in the patients on placebo during follow-up. Because muscle contraction plays a central role in sustaining headaches in individuals with CTTH, it would be reasonable to expect that drugs with muscle-relaxing properties would be superior to placebo. This was not the case in our study, which supports the view that psychophysiological and other mechanisms are of more importance in sustaining CTTH than sustained muscle contraction. Our results do not rule out the view that peripheral myofascial mechanisms may play a role in the development of CTTH.

Our findings do not match the findings of the placebo-controlled study by Fogelholm and Murros; however, the standard formulation of tizanidine was used to treat CTTH in their study.[6] The efficacy of the standard formulation was compared with placebo in their randomized, double-blind, crossover study, in which 37 women participated. Two 6-week treatment periods were separated by a 2-week washout phase. The initial dose was 2 mg three times a day. If necessary, this was increased up to 6 mg three times a day. The efficacy was measured by VAS, the number of days free of headache, and the number of analgesic tablets needed. By all these measures, the standard formulation was statistically significantly more effective than placebo. Some differences should be noted between these studies. First, the sample size of the study by Fogelholm and Murros was relatively small. However, due to the crossover design, the power of the study was comparable with the present study. Second, instead of averaging the VAS information when comparing treatment efficacy, Fogelholm and Murros used cumulative sums of VAS scores in their analysis. Different drug formulations may affect the results as well. Side effects of tizanidine hydrochloride, although generally mild, are possibly more prevalent in those taking standard formulation (tizanidine) than the MR formulation (tizanidine MR) with similar daily doses. This may have caused more unblinding in the Fogelholm and Murros study. Conversely, the standard formulation of tizanidine causes high plasma concentration peaks, and could be, in fact, more active than the MR formulation to treat CTTH. Taking the drug in the evening may not be as effective as taking it in divided doses during the day. It should be pointed out that maximum plasma concentrations of the modified release formulation are usually reached within 5 to 6 hours and the peak concentration is only about 40% of the concentration obtained when equal daily amounts of the standard formulation are given in three divided doses.[1] Also, the MR formulation is less bioavailable than the standard formulation: patients taking 12-mg tizanidine MR once a day are exposed to an amount of tizanidine comparable to an amount of 2-mg tizanidine standard formulation three times a day.

To summarize, the MR formulation of tizanidine up to 12 mg taken in the evening is not superior to placebo in treating individuals with CTTH. The placebo was as effective in the treatment of this chronic disorder. This finding does not abrogate the previous findings on the positive effect of the standard release formulation of tizanidine to treat chronic TTH.

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