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ORIGINAL

Cinnarizine in refractory migraine prophylaxis: efficacy and tolerability. A comparison with sodium valproate

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Abstract This was a double-blind clinical trial designed to assess the efficacy and safety of the cinnarizine (CIN) in patients with migraine who were refractory to propranolol and tricyclic antidepressants in comparison with sodium valproate (SV) to investigate whether CIN could be at least as effective as SV. A total of 125 patients were treated in a treatment period of 12 weeks. All patients had at least one intake of trial medication and 2-week post baseline efficacy observation which all were included in the ITT analysis. Of the 125 subjects treated, 46 discontinued prematurely: 25 from the CIN and 21 from the SV group. The main reasons for premature discontinuation were: lost to follow up (25/46, 63.2%), insufficient response (16/46, 20%), and adverse events (5/46, 12.8%). No statistically significant inter-group differences in the number of discontinuation was observed ($p > 0.05$). In both groups, number of attacks, intensity, and duration of attacks significantly decreased ($p < 0.05$). No statistically significant inter-group differences were observed regarding the mean number of attacks, duration, and intensity of migraine attacks for any of the time intervals analysed, except for the mean reduction of third and fourth visits intensity from baseline which were significantly different in two groups ($p < 0.05$), with the CIN group showing more reduction. Analysis of the number of responders showed that in the CIN group 61.2% subjects were responders, and 63.8% in the SV group. No statistically significant differences between the treatment groups were found for any of the secondary parameters. Overall 26 subjects reported one or more adverse events during the study period: 13 subjects in each group. Five subjects discontinued prematurely due to adverse events; two in the CIN group with significant weight gain, and 3 in the SV group with significant weight gain and severe tremor. These results suggest that CIN is an effective and safe prophylactic agent even in severe migraine headache.

Keywords Migraine prophylaxis · Cinnarizine · Sodium valproate

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Introduction

Migraine is one of the most common headache conditions known to mankind, with prevalence of 17% for women, 6% for men, and 4% for children [1], and often associated with significant disability and impaired quality of life, adversely affecting daily activity and work related productivity for many persons [2]. Prophylactic treatment for migraine is used in cases where frequency and severity of attacks warrant such an intervention. The most frequently used drugs for migraine prevention are β-blockers, calcium channel blockers, serotonin antagonists, monoamine oxidase inhibitors, and anticonvulsant agents [3–6].

Cinnarizine (CIN) is an L-type calcium channel blocker, which inhibits contractions of vascular smooth muscle cells [7], directly inhibits vestibular hair cells stimulation [8], and has antihistaminic actions [9]; all these mechanisms can potentially contribute to its preventive effects on migraine.

In 1993, 1999 and more recently in 2001, The Italian Guidelines for the treatment of headache included the CIN among the drugs with the higher levels of recommendation (first choice drug in 1993 and 1999, group II level of recommendation in 2001, comparable for instance to metoprolole) [10, 11]. Interestingly, the CIN is not mentioned in the guidelines produced by other scientific societies [11–14] and apart from few "local" reports [15–19] no study has systematically evaluated this drug in migraine prophylaxis.

Rossi et al. [17] first showed the effectiveness and tolerability of CIN in migraine prophylaxis after the publication of international headache society (IHS) diagnostic criteria and guidelines for clinical trials [20, 21]. Amelin et al. [19] reported a great reduction in migraine attacks frequency when studying vertigolitic effect of CIN in a group of migraneurs. In a recently published open-label trial, we showed significant improvement in migraine headache frequency, duration, and intensity of headache [18].

Several anticonvulsants have also been investigated in the treatment of migraine, which sodium valproate (SV) has been shown to be more effective than others [22]. In clinical trials, about 30–50% of patients taking SV have achieved a 50% reduction in headache frequency [23–25].

No studies are available comparing CIN with SV for prevention of migraine headache.

The aim of this trial was to demonstrate the efficacy and safety of the CIN in patients with migraine who were refractory to propranolol and tricyclic antidepressants, in comparison with SV to investigate whether CIN could be at least as effective as SV.

Subjects and methods

Overall trial design and plan

We used a comparative trial characterized by a run-in phase followed by a double-blind period during which the subjects received either CIN or SV. We did not use any placebo because the subjects have had intractable migraine and it was immoral to use no drug during 12 weeks. The trial was approved by the ethics committee of Tehran University of Medical Sciences, and all patients were informed consent about the aim of the study and gave informed consent prior to entering the study.

The trial started with a no medication run-in phase of 4 weeks, in which, the patients were allowed to use analgesic drugs to treat acute migraine attacks. This phase was included in the study to familiarize patients with trial procedure, establish a subject's competence to correctly fill in the diary, and having a baseline data. At the end of this screening phase, subjects were randomized to CIN 75 mg or SV 600 mg, and the 12 week double-blind treatment phase was started, during which visits were scheduled at 2, 4, 8, and 12 weeks. A total of 125 patients were expected to be needed to prove that CIN was at least as effective as SV.

Inclusion criteria was as follows:

Male or female. Age 16–60 years;
Having experienced 3–10 migraine attacks every month for the preceding 2 months;
Migraine present for at least 1 year;
Migraine with or without aura as defined by the HIS [21];
Onset of migraine before the age of 50 years.

Exclusion criteria were:

Use of prophylactic migraine therapy in at least one preceding month;
Previous or current history of alcohol addiction or drug abuse including analgesics;
Occurrence of interval headaches;
Extra pyramidal disorders;
Serious disease (diabetes, serious hepatic, renal, cardiovascular or malignant illness); Pregnancy, lactating or child-bearing potential without adequate contraception.
Known hypersensivity to CIN or SV.

Treatment

After run-in phase one group of subjects received CIN tablets and another group received SV tablets three times daily for 12 weeks. Both drugs were white and round, but not exactly similar. All tablets were put in the same drug packages. Random allocation of patients to study groups were provided by balanced block randomization using block of six, in that both patient and physician were not aware of the treatment type that the patient received. At the start of the trial (visit 0), a complete medical history and specific migraine history was recorded and a general physical and neurological examination, blood counts and liver function tests were performed. The subjects were given a dairy in which all migraine attacks, duration of attacks (hours), intensity of attacks (assessed by a 10-score Visual Analog Scale (VAS) with 0 indicating no pain and 10 indicating the worst pain imaginable), number of days without migraine, and time between two consecutive attacks had to be recorded. From visit 1 (start of double-blind period) through visit 5 (end of week 12), the subject's dairy was checked and collected. Laboratory test included blood count and liver function tests also performed at the end of the trial. Refractory headache was classified in those who had been refractory to all previous forms of therapy including β-blocker and anti depressants.

The main end points were the mean attack frequency per 4 weeks in the entire double-blind period and the number of responders. The percentage of responders defined as subjects for whom the attack frequency decreased by ≥50% compared to run-in per visits in the double-blind period. Mean duration of migraine attacks, mean intensity of the attacks, mean number of days without migraine, and mean time between two consecutive attacks were second parameters.

The factors considered to have a possible prognostic value for therapeutic responsiveness to each drug were type of migraine (with or without urea), sex, age, family history (maternal or paternal), frequency, duration, and intensity of migraine attacks, age of migraine onset, duration of migraine history, presence of concomitant symptoms (nausea vomiting, photophobia and phonophobia), and resistance to prophylactic treatment.

From visit 1 on, the subjects was asked whether he/she had experienced any adverse events. Special attention was paid to the occurrence of sedation, weight gain and extra pyramidal symptoms.

Statistics

All randomized subjects with at least one intake of the trial medication and one post baseline efficacy observation period of at least 2 weeks were defined as intention-to-treat populations. If a 50% decrease in migraine frequency is considered to be a clinically response on the basis of previous estimates of SD of 2.50, and accounting for pairwise comparisons, subjects per group were expected to be needed to prove that CIN was as effective as SV at the 5%-level, with a power of 80%. Statistical analysis was based on an intention-to-treat principle.

Baseline between-group comparability with respect to demographic variables and efficacy parameters were assessed. Descriptive statistics for each treatment separately and for the total population were provided. The Student's t test for independent samples and analysis of variance with repeated measures over time was applied to investigate treatment comparability with respect to continues variables. Paired-Student's t test was performed to study the comparability between basal and post-treatment periods. Results are expressed as mean and $p < 0.05$ was considered statistically significant. The analysis were done on a personal computer using SPSS for windows, and confidence interval analysis software.

Results

The trial was run from May 2002 to April 2004. In total 125 subjects were recruited in the study and all were randomized; 67 were assigned to CIN 75 mg and 58 to SV 800 mg. All patients had at least one intake of trial medication and 2-week post baseline efficacy observation which all were included in the ITT analysis.

Of the 125 subjects treated, 46 discontinued prematurely: 25 from the CIN and 21 from the SV group. The main reasons for premature discontinuation were: lost of follow up (25/46, 63.2%), insufficient response (16/46, 20%), and adverse events (5/46, 12.8%). No statistically significant inter group differences in the number of discontinuation was observed ($p > 0.05$).

The demographic data of the 125 subjects randomized and treated was shown in Table 1. Over all 80.8% of the subjects were female, and the median ages in the two groups was 34 years with minima and maxima ranging from 13 to 60 years. Demographic data were not significantly different between the two groups.

Table 2 summarized the efficacy parameters in the ITT population per visits during the double-blind period in two treatment groups. Analysis of the number of responders showed that in the CIN group 41 (61.2%) subjects were

Table 1 Characteristics of patients by treatment group at baseline

Baseline characteristics	Cinnarizine ($n = 67$)	Sodium valproate ($n = 58$)
Sex (male/female)	11/56	13/45
Mean age (years)	34.5 (13–60)	33.6 (16–55)
Mean age of migraine onset (years)	25.5 (9–45)	22.5 (10–40)
Family history (positive)	41 (61.2%)	35 (60.3%)
Mean attack frequency (n)	7.4 (3–10)	6.9 (3–10)
Mean duration of attack (h)	14.6 (4–24)	14.3 (4–24)
Mean intensity of the attack (VAS)	8.4 (4–10)	8.1 (4–10)
Mean number of days without attacks (h)	22.6 (20–27)	23.1 (20–27)
Mean time between two consecutive attacks (h)	4.6 (3–10)	5.1 (3–10)
Concomitant symptoms		
Nausea	59 (88.1%)	51 (87.9%)
Vomiting	28 (41.8%)	25 (43.1%)
Photophobia	41 (61.2%)	40 (69.0%)
Phonophobia	54 (80.6%)	42 (72.4%)
Response to propranolol		
Without response	10 (14.9%)	7 (12.1%)
Weak	34 (50.7%)	30 (51.7%)
Partially response	23 (34.3%)	21 (36.2%)
Response to TCA		
Without response	8 (11.9%)	9 (15.5%)
Weak	36 (53.7%)	29 (50.0%)
Partially response	23 (34.3%)	20 (34.5%)

VAS visual analogue scale

Table 2 Comparison of efficacy parameters in the intention-to treat (ITT) population after therapy and the differences with baseline

Efficacy parameters	After therapy		Intergroup differences (CI 95%)
	Cinnarizine $n = 67$	Sodium valproate $n = 58$	
Mean attack frequency (n), mean ± SD	3.12 ± 1.70	3.00 ± 1.61	0.12 (−0.62, 0.87)*
Percentage of responders[a] (%)	41 (61.2%)	37 (63.8%)	–
Mean duration of the attack (h), mean ± SD	10.01 ± 7.10	8.97 ± 7.06	1.03 (−2.16,4.23)*
Mean intensity of the attack (VAS), mean ± SD	5.03 ± 1.74	5.36 ± 2.03	−0.32 (−1.18,0.53)*
Mean number of days without attacks (days), mean ± SD	26.86 ± 1.84	26.90 ± 1.80	−0.39 (−0.086,0.78)*
Mean time between two consecutive attacks (h), mean ± SD	12.26 ± 6.31	12.06 ± 6.33	0.19 (−2.66,3.05)*

VAS visual analogue scale

*No significant differences. $p > 0.05$

[a] Responders: decreased in attack frequency with at least 50% as compared to run-in

responders, and 37 (63.8%) in the VS group. Statistical testing showed that CIN treatment was at least as effective as SV with respect to frequency of migraine attacks decreased, and the percentage of the responders.

Fig. 1 summarize the mean number of attacks at the baseline, per visits during the double-blind period and 2 day week (2nd visit). Although the onset of significant clinical effect was first noticed in the 2-week period (55% in both groups), the maximum improvement in headache frequency was achieved in 64% of patients in CIN and 59% of patients in VS group at the end of 12 weeks. A similar observation was also noted in headache duration and intensity.

For the changes in duration of migraine attacks when compared to run-in, no statistically significant differences were noted, and no time effects was observed in any of the treatment groups. For changes in the intensity of attacks when compared with run-in, statistically significant inter group differences were observed at third and fourth visits.

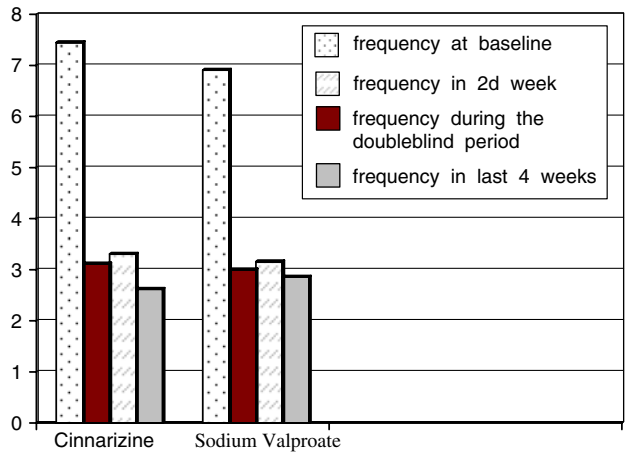

Fig. 1 Mean number of attacks in the baseline period, per visits during the double blind period, in 2nd week, and the last 4 weeks of treatment

In the CIN group the intensity of attacks was decreased by 3.3 at 3 day visit and 4 at fourth visit, compared to a reduction of 2.1 at 3 day visit and 2.6 at fourth visit in SV group.

The mean days free of headache ranged from 22 days at run-in to 27 days at endpoint. Inter group comparison of changes at all time points again showed no statistically significant differences between the treatments. No significant intergroup differences in the mean time between two consecutive migraine attacks were observed, nor did analysis of differences with run-in demonstrated statistically significant intergroup differences.

Over all 26 subjects reported one or more adverse events during the study period: 13 subjects in each group. The most frequent adverse events were weight gain, somnolence, hair loss, vertigo, nausea, vomiting, tremor, abdominal pain. Five subjects discontinued prematurely due to adverse events; two in the CIN group with significant weight gain, and three in SV with significant weight gain and sever tremor. No significant hematological or hepatic side effects were seen in the subjects of both groups at the end of the trial.

Discussion

This was a double-blind trial designed to assess the efficacy and tolerability of CIN in the prophylaxis of refractory migraine in comparison with the frequently used drug SV. We used no placebo arm in this study because it was immoral to use no drug in the subjects with intractable headache.

A total of 125 subjects were treated (treatment period was 12 weeks) and 46 subjects discontinued the trial prematurely but after visit 1, so all subjects were included in the ITT analysis. However, it could be considerable as a defect that 46 subjects discontinued, it maybe because of

severe headache in our subjects who had less compliance to continue their treatment.

For two efficacy parameters, mean attack frequency per 4 weeks in the entire double-blind period and the number of responders, CIN was as effective as SV. No statistically significant differences between the two treatment groups were found for any of secondary parameters ($p > 0.05$): mean duration of migraine attacks, mean intensity of attacks, mean number of days without migraine, and mean time between two consecutive migraine attacks. The mean reduction of 3 day and fourth visit intensity from baseline were significantly different in two groups ($p < 0.05$), with CIN group more reduction, which may be related to more effectiveness of CIN than VS after 12 weeks of treatment.

To the best of our knowledge, no other studies are available comparing CIN with SV, and this is the first randomized double-blind clinical trial to compare the effect of CIN and SV on migraine headache prevention. Also as mentioned before, there are a few local reports of evaluating CIN in migraine prophylaxis; Rossi et al. [17] in an open-label trial of 80 patients treated with CIN in which they reported a mean reduction of 58% in migraine monthly frequency and at least 66% improvement in 71% patients. Amelin et al. [19] in their series of 28 vertigo patients with migraine, also reported 65% reduction in migraine monthly frequency. A recently published open-label trial of ours showed a reduction of 75% in migraine monthly frequency and by 50% improvement in 86% patients [18].

The present results of 63.5% reduction in monthly frequency and 61.2% responders are consistent with previous studies, which demonstrate the efficacy of CIN in the prophylaxis of refractory migraine headache.

In the other hand, in recent years, SV has been shown to have encouraging results in the prophylactic treatment of different headache types [22, 24, 25–28]. Erdemoglu et al. [22] in a study on 127 patients with refractory migraine headache showed 50% improvement in 67% patients. The beneficial effect of 60% reduction in intensity of attacks was also observed in their study without any changes in the duration of attacks. Some of other studies demonstrated improvement in headache frequency, intensity, and duration of headache [22, 26, 28]. The results of current study with a mean reduction of 53.6% in monthly frequency and 63.8% improvement in patients, in consistence with previous studies, support the efficacy of SV in the prophylaxis of migraine.

With respect to these results and no statistically significant differences between the two treatment groups in efficacy parameters, CIN is as effective as SV in prophylaxis of refractory migraine attack.

In both groups, also the onset of clinical effect was evident in the 2 day week (55% in both groups), the maximum effect was observed in the 12th week (64% in CIN group and 59% in VS group). Although these findings were also noted in other studies [18, 22, 29], the onset of effect was reported in the 4-week period which was not significant. The reason for the early onset of effect and the delayed of onset of maximum effect could not be explained with the prophylactic properties of these drugs. Therefore, CIN and SV should be used for more than 8 weeks to notice the maximum effect. It may be assumed there is an additional effect over 12 weeks and future controlled studies should be extended to 16 weeks or longer.

No statistically significant effect of predictive factors included type migraine (with or without urea), sex, age, family history (maternal or paternal), frequency, duration, and intensity of migraine attacks, age of migraine onset, duration of migraine history, presence of concomitant symptoms (nausea vomiting, photophobia and phonophobia), and resistance to prophylactic treatment, was observed.

Over all 20% of subjects reported adverse events in both group with no significant differences ($p > 0.05$). All events were mild and moderate except for five patients (two in CIN and three in SV group), which lead to discontinued the study. In a previous study, in elderly people, cases of aggravation or an appearance of exterapyramidal symptoms have been described during prolonged therapy with CIN [30], but as migraine prevalence decline after 40 years, this complication usually is not the case. Although it was reported that monitoring of drug levels and liver function tests is not needed, it may be essential to prevent serious liver damage. Clinical examination or liver function tests detected no cases of hepatic injury. The most valuable test for adverse events is clinical observation of the patient.

The results of this double-blind clinical trial on refractory migraine headache to propranolol and tricyclic antidepressants showed that CIN is an effective and safe prophylactic agent even in severe migraine headache after 12 weeks of treatment. Also the onset of significant effect in 2 day week of treatment is notable, and more reduction of headache intensity in CIN than SV. Future controlled trials expended longer would also support the effectiveness and safety of CIN in patients with refractory headache.

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