

# Prophylactic Activity of Cyproheptadine and Bellergal on Migraine Headache

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## Abstract

**Background:** A wide range of preventive medications for migraine attacks, with varying efficacy is currently in use. Studies comparing the efficacies of these drugs would be of value in the proper treatment of the disease. The present study compared the frequency, duration and intensity of migraine attacks during and following treatment with cyproheptadine (4 mg, twice daily) or Bellergal (belladonna 0.1 mg, ergotamine 0.3 mg and phenobarbital 20 mg).

**Methods:** 118 patients 15 to 45 year-old with migraine headaches were randomly allocated to groups I (n=36), II (n=40) and III (n=42) and treated during three consecutive phases of 45 days. In phase one all groups received two oral placebo tablets daily. In phase two, group I continued with placebo, groups II and III received cyproheptadine (4 mg, twice daily) and Bellergal (three tablets daily), and finally, in phase three all groups were treated with placebo, respectively.

**Results:** Cyproheptadine and Bellergal treatments significantly reduced the frequency, duration and intensity of migraine attacks. These parameters remained low during phase three (placebo) in cyproheptadine treated patients as compared to those who only received placebo. But there was a rebound effect following discontinuation of Bellergal.

**Conclusion:** Cyproheptadine and Bellergal seem to preventive migraine attacks. Cyproheptadine is a preferred choice because its effects were partially preserved following withdrawal.

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**Keywords •** Cyproheptadine • Bellergal • migraine

## Introduction

**M**igraine is a chronic condition of recurring headaches of moderate to severe intensity, affecting 6% of men, 18% of women and may last for part of a day or as long as few days.<sup>1,2</sup> The prevention of migraine headaches by drug therapy is acute or chronic and both approaches are often required in patients who experience frequent severe headaches.<sup>3</sup> Indications for migraine prevention therapy include two or more attacks per month which procure disability.<sup>3</sup>

A wide range of preventive treatments with varying efficacy is currently in use and the range of these drugs is expanding. Alpha<sub>2</sub> agonists, anticonvulsants, antidepressants, beta-

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blockers, calcium-channel blockers and non-steroidal anti-inflammatory drugs, etc, are used for preventive therapy.<sup>3,4</sup> Cyproheptadine is a serotonin antagonist, which is recognized as clinically effective in prevention of migraine attacks.<sup>5</sup>

This study was undertaken to compare the effects of cyproheptadine and Bellergal (including ergotamine, belladonna alkaloids and phenobarbital) on the frequency, duration and the intensity of migraine attacks. Since the curative effects of these drugs are not clear, the frequency, duration and the intensity of migraine attacks before drug usage and after withdrawal were also compared.

### Patients and Methods

This work was approved by the Research Ethical Committee of Shahrekord University of Medical Sciences. Proper information regarding the use of medications was provided to the patients and an informed consent was obtained. 118 patients with migraine headache (ages ranging from 15 to 45 years) randomly selected from the author's neurology private clinic (Shahrekord, Iran). Eligible patients had to meet the diagnostic criteria for migraine as defined by the International Headache Society (IHS).<sup>6</sup> Accordingly, a patient must have at least five headache attacks lasting for 4-74 hrs with at least two of the following symptoms; lateralized headache, pulsating pain of moderate to high intensity, exacerbation by effortful physical activity, nausea and/or vomiting, photo- and phono-phobia.<sup>6</sup>

A minimal duration of the disorder had to be one year and at least two attacks had to take place one month before participating in the study. Exclusion criteria included those patients with secondary headache, neurological disorders, last two months trials of medication for prophylaxis of migraine, severe medical or psychiatric illness, and use of hormonal contraceptives, pregnancy, analgesic usage for other illnesses, or drug abuse. Patients unable to complete a headache diary or to differentiate various headache types were also excluded.

### Patients and Methods

Throughout the study, the patients and the investigator were blind to the administered medications. Cyproheptadine (4 mg, twice daily) and Bellergal tablets (0.1 mg belladonna, 0.3 mg ergotamine and 20 mg phenobarbital/tablet) were used to prevent migraine attacks obtained from Darupakhsh and Sobhan Companies, Tehran, Iran. Tablets (both drugs and placebo) were put into identical packets

and randomly coded 1, 2 or 3 by a pharmacist without knowing the content. Tablets were prescribed by the neurologist through code numbers up to the end of the study.

Patients were randomly allocated into three groups and treated in three consecutive phases, each lasting 45 days. During phase one, patients of all groups received two placebo tablets daily. During phase two which started at day 46 and ended at day 90, group I continued with placebo (n=36), group II (n=40) received two cyproheptadine tablets daily (8 mg/day), and group III (n=42) received three Bellergal tablets daily. As washout period, starting at day 91, all patients stopped medication for eight days. Phase three started at day 99, after washout period, and again all patients received placebo medication until day 144. During the course of the study patients were free to take one or two tablets of acetaminophen-codeine when needed.

Patients had a diagnostic headache diary to record their headache symptoms, such as the type, the frequency, duration and the intensity. They were also asked to record and report to the physician in charge of the study the intensity of their headache on an arbitrary scale (10 scale point) with one reflecting the least intensity (absence of effect on daily activity), and 10 reflecting the most intensity (preventing daily activity).

### Statistical analysis

Data are presented as mean±SD. Analysis of the data involved one-way analysis of variance (ANOVA), Tukey's HSD, Kruskal-Wallis and multiple comparison tests.

### Results

The mean±SD ages of patients participated in groups I, II and III were 29.7±8.1 yrs, 29.2±7.8 yrs and 31.9±8.4 yrs, respectively and were not statistically different. Before participating in the study, 83.1% of patients had migraine without aura and 16.9% with aura with the frequency and duration of migraine headaches of 4±1.8/month and 23.1±10.9 hrs respectively.

**Table 1:** Effects of placebo treatments (phase 1, 2 and 3) on the frequency (FR; attacks/month), duration (DU; hrs) and intensity (IN; 1-10) of migraine attacks of group I.

Phase	FR	DU	IN
1 (Placebo)	3.51±2.32	21±8.60	7.21±2.05
2 (Placebo)	4.80±2.03	26.4±8.98	7.34±2.86
3 (Placebo)	3.94±1.36	23.5±7.90	8.02±1.83

Data are presented as mean±SD.

p>0.05 when three phases compared.

Tables 1, 2 and 3 show the values of frequencies, durations and intensities of migraine attacks during placebo treatments in group I dur-

**Table 2:** Effects of placebo treatments (phase 1 and 3) and cyproheptadine treatment (cypro; phase 2) on the frequency (FR; attacks/month), duration (DU; hrs) and intensity (IN; 1-10) of migraine attacks of group II.

Phase	FR	DU	IN
1 (Placebo)	3.5±1.3	21.0±8.6	7.2±2.0
2 (cypro)	1.9±1.1*	13.6±8.3*	5.1±3.0*
3 (Placebo)	2.3±1.3*	16.9±9.4*	5.1±3.1*

Data are presented as mean±SD.

\* Denotes statistically significant (p<0.05) from the same variables as of phase 1.

ing all three phases and in groups II and III during phase 1. The values of these parameters were not statistically different from each other, where as these parameters decreased significantly during cyproheptadine treatment (p<0.05; Table 2). Following drug withdrawal (phase 3), the frequency, duration and intensity of attacks in group II (cyproheptadine) did not change significantly (Table 2). In group III these parameters decreased significantly during Bellergal treatment (p<0.05; Table 3) but returned back to the pretreated levels after withdrawal (Table 3). Comparison of the results of groups II and III revealed that only the reduction duration of migraine attacks in cyproheptadine treated group (table 2) was more pronounced than of Beller-

**Table 3:** Effects of placebo treatments (phase 1 and 3) and Bellergal treatment (phase 2) on the frequency (FR; attacks/month), duration (DU; hrs) and intensity (IN; 1-10) of migraine attacks of group III.

Phase	FR	DU	IN
1 (Placebo)	4.8±2.0	26.4±9.0	7.3±2.9
2 (Bellergal)	2.7±1.9*	19.3±9.1*	5.8±2.9*
3 (Placebo)	3.2±1.9	20.4±9.7	6.4±2.6

Data are presented as mean±SD.

\*Indicate significantly different from the same variables as of phase 1 at p<0.05

gal group (P<0.05, Table 3).

## Discussion

The causes of migraine headaches and the mechanisms of action of antimigraine drugs are not fully understood. However, there are clinical and experimental evidences indicating that extracerebral arterial vasodilation, extradural neurogenic inflammation, and decreased inhibition of central pain transmission are involved in the pathogenesis of the migraine headache.<sup>8</sup> Serotonin is one of the known neurotransmitters that participate in the above mentioned processes. Therefore, cyproheptadine, which is a competitive serotonin receptor blocking agent, might exert its antimigraine effects by blocking antiserotonergic serotonin receptors.<sup>9</sup> Its antihistamine and anticholinergic activity may also potentate the antimigraine activity of this drug.<sup>9</sup>

The frequency, duration and intensity of migraine attacks were reduced by both cyproheptadine and Bellergal (Tables 2 and 3). The prophylactic effects of cyproheptadine on migraine attacks are well established,<sup>7</sup> whereas the efficacy of Bellergal is in question.<sup>3</sup> This study demonstrated that cyproheptadine might be a suitable antimigraine medication for preventing migraine attacks, or at least might be suitable alternative for patients who can not tolerate other antimigraine drugs.

Little evidence exists about the prophylactic effects of ergotamine alone, or in combination with belladonna alkaloids and phenobarbital, on migraine attacks but its abortive effects of is indisputable.<sup>8</sup> However, a rebound effect was observed following cessation of Bellergal usage. The reduction in frequency, duration, or intensity of attacks in phase three, in cyproheptadine group may be considered as "free-attack effect", a phenomenon which occurs following prevention of attacks in epilepsy. However, there was statistically no difference between phase three and phase one, in Bellergal group. It means, reduction of migraine attack, following an attack-free period, is not general and is specific for cyproheptadine, in this study. This specific effect is not clear for other drugs, and needs more investigations. The mechanism involved in this phenomenon, in cyproheptadine effect is not known. Serotonin is a neurotransmitter, which seems to be largely involved in pathogenesis of migraine headache.<sup>8</sup> Cyproheptadine is a serotonin antagonist. Therefore, inhibition of serotonin receptors, by cyproheptadine, might have caused a change in serotonin receptor quantity or quality (sensitivity). This phenomenon needs also more investigations.

Both medications demonstrated high anticholinergic and sedative activity. However, in global the side effects of cyproheptadine were less than Bellergal. Therefore, cyproheptadine due to higher efficacy as a preventive therapy, preservation of effectiveness following discontinuation, and less side effects seems to be preferred medication compared to Bellergal for prevention of migraine attacks. It should be noted that the choice of the preventives to prescribe should be based on the patient's physical and mental conditions, too. For example, a patient subject to low weight would be more suitable for cyproheptadine and a patient subject to down moods and insomnia would be more suitable for amitriptyline.

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### References

- 1 Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001; 41: 646-57.
- 2 Lipton RB, Diamond S, Reed M, et al. Migraine diagnosis and treatment: results from the American Migraine Study II. *Headache* 2001; 41: 638-45.
- 3 Snow V, Weiss K, Wall EM, Mottur-Pilson C. American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med* 2002; 137: 840-9.
- 4 Kanieki R. Headache assessment and management. *JAMA* 2003; 289: 1430-4.
- 5 Rao BS, Das DG, Taraknath VR, Sarma Y. A double blind controlled study of propranolol and cyproheptadine in migraine prophylaxis. *Neurology India* 2000; 48: 223-6.
- 6 Headache Classification Committee of International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgia and facial pain. *Cephalalgia* 1988; 8: 1-96.
- 7 Lewis DW, Scott D, Rendin V. Treatment of pediatric headache. *Expert Opin Pharmacother* 2002; 3: 1433-42.
- 8 Spierings-Egilius LH. Pathogenesis of migraine attack. *Clin J Pain* 2003; 19: 255-62.
- 9 Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalalgia* 2002; 22: 491-512.