

## GABAPENTIN IN THE PROPHYLAXIS OF CLUSTER HEADACHE: AN OBSERVATIONAL OPEN LABEL STUDY

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**SUMMARY** – Cluster headache is an extremely painful syndrome that occurs more frequently in men. Although periodic in most cases, cluster headache has a considerable impact on the patient quality of life. Acute therapy is usually not sufficient and most patients warrant prophylactic treatment. The aim of this study was to evaluate the efficacy and safety of gabapentin as prophylaxis in patients with cluster headache previously successfully or unsuccessfully treated with other prophylactic medications. The study included 14 patients, 9 men and 5 women (mean age  $42 \pm 15$  years). Gabapentin was gradually introduced; the maintenance dose was in the range from 900 mg to 2400 mg: 900 mg/day in 6, 1200 mg/day in 2, 1800 mg/day in 4 and 2400 mg/day in 2 patients. The mean duration of treatment was 3.5 (range 2-5) months. Within 1-2 weeks, patients reported response to treatment. The mean number of headache days/4 weeks was reduced from 378 (mean 27) at baseline to 210 (mean 15) at the end of follow up, yielding a reduction by 12 headache days/4 weeks or by 44.94% in headache frequency. Pain intensity was decreased by 25% in 1 (7.14%) patient, by 50% in 8 (57.14%) and by 75% in 3 (21.4%) patients, whereas 2 (14.28%) patients were non-responders. Upon completion of gabapentin therapy, there were no recurrent in treated patients. Adverse events were reported in 8/14 (57.14%) patients and were generally of mild to moderate severity. The most frequently reported adverse events were drowsiness, dizziness, slowness and constipation. There were no drop-outs due to adverse events.

**Key words:** *Cluster headache – drug therapy; Cluster headache – prevention and control; Acetic acid – therapeutic use; Analgesic – therapeutic use; Migraine – drug therapy*

### Introduction

Cluster headache is an extremely painful syndrome that occurs more frequently in men; the estimated prevalence is less than 1%<sup>1</sup>. Although periodic in most cases, cluster headache has a considerable impact on the patient quality of life<sup>2</sup>. Most patients with cluster headache warrant prophylactic treatment, which usually includes corticosteroids, verapamil and lithium<sup>3,4</sup>. Recently, antiepileptic drugs (AEDs) have also been proposed in prophylaxis, however, there is a

general lack of such studies<sup>3,4</sup>. The aim of this study was to evaluate the efficacy and safety of gabapentin as prophylaxis in patients with cluster headache previously successfully or unsuccessfully treated with other prophylactic medications.

### Patients and Methods

It was an open prospective study that included patients with episodic cluster headache attending the Headache Clinic at our University Department of Neurology. Cluster headache was defined according to the ICHD-2 criteria<sup>5</sup>. Patients were included if they had suffered at least three episodic cluster periods in previous years, if previous prophylactic treat-

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ment with other medications had failed or had to be discontinued due to adverse events (previous prophylactic treatment mostly included corticosteroids and/or verapamil); patients agreed to take no concurrent prophylactic treatment for headaches (pharmacological or non-pharmacological); patients had no serious concomitant diseases and were willing to be available for follow up for at least 3 months. All patients gave their informed consent.

Gabapentin was started with one 300 mg capsule and increased by 300 mg daily up to 900 mg daily; further increase was made if necessary up to the maximum dose of 2400 mg. A stepwise increase of medication was made according to the presence of adverse events. Upon introducing gabapentin in the treatment, patients were instructed to keep a diary and note all days with headache, decrease in headache intensity if present, increase of gabapentin dosage, acute medications taken for cluster attacks, and occurrence of adverse events. The patients were told to use their usual therapy for acute attacks, which included non-steroid anti-rheumatics and triptans.

The primary efficacy endpoint was the change from baseline in the mean monthly (28 days) number of days with cluster attacks, decrease of headache intensity and reduction of the mean number of acute medication use. The change in headache intensity was recorded as a percentage (no change, and decrease by 25%, 50%, 75% or 100%). Assessment of safety and tolerability included physical, neurologic and laboratory examinations, and spontaneous reports of adverse events.

On statistical analysis, Wilcoxon's signed rank test was used to compare baseline and end-point values.

## Results

The study included 14 patients, 9 men and 5 women (mean age 42±15 years). The maintenance dose of gabapentin in all patients was in the range from 900 mg to 2400 mg: 900 mg/day in 6, 1200 mg/day in 2, 1800 mg/day in 4 and 2400 mg/day in 2 patients. The dose of gabapentin was not increased over 2400 mg because an improvement was achieved or adverse events occurred at this dosage.

Patients were receiving gabapentin according to the duration of attacks they

had experienced in previous cluster periods, which was in our patients from 1 to 3 months, followed by one month in which the dose was gradually tapered off. The mean duration of treatment was 3.5 (range 2-5) months. Within 1-2 weeks, patients reported response to treatment. The mean number of headache days/4 weeks was reduced from 378 (mean 27) at baseline to 210 (mean 15) at the end of follow-up, i.e. a reduction by 12 headache days/4 weeks, yielding a 44.94% reduction in headache frequency. Pain intensity was decreased by 25% in 1 (7.14%) patient, by 50% in 8 (57.14%) and by 75% in 3 (21.4%) patients, whereas 2 (14.28%) patients were non-responders. Upon completion of gabapentin therapy, no recurrent attacks occurred in the treated patients. All study patients were followed-up for at least 3 months (mean follow up, 6 months). The range of gabapentin doses and reduction of pain intensity are shown in Table 1.

Before starting the treatment with gabapentin, patients were taking at least one medication (analgesics or triptans) daily to treat their attacks. The exact number of medications previously used for cluster attacks was not available; however, based on patient recall, a reduction of acute medication use by at least 50% was reported in 11 patients, whereas one patient had no need for acute medication anymore.

Adverse events were reported in 8/14 (57.14%) patients and were generally of mild or moderate severity. The most frequently reported adverse events were drowsiness 5/14 (35.7%), dizziness 3/14 (21.4%), slowness 1/14 (7.1%) and constipation 1/14 (7.1%). There were no drop-outs due to adverse events.

## Discussion

In general, there is a lack of multicenter randomized double-blind trials of antiepileptic drugs (AEDs),

*Table 1. (A) Range of gabapentin doses in patients with cluster headache; and (B) reduction of headache intensity*

A) Gabapentin dosage (mg)				
	900	1200	1800	2400
N=14 (%)	6 (31.57)	2 (14.28)	4 (28.57)	2 (14.28)
B) Reduction of pain intensity by %				
	0%	25%	50%	75%
N=14 (%)	2 (14.28)	1 (7.14)	8 (57.14)	3 (21.4)

especially gabapentin, as a prophylactic treatment in patients with cluster headache. The reasons for this paucity of evidence based data are the low prevalence of cluster headache; cluster periods are usually relatively short and show a tendency of spontaneous remission, which may bias study results. Although double-blind placebo-controlled studies provide unbiased results, they are sometimes difficult to carry out; therefore, open-label studies offer additional data on the efficacy of pharmacological or non-pharmacological treatment. Placebo controlled studies in cluster patients would be unethical due to extremely troublesome symptoms which patients experience and because other medications have already been proven in trials to be efficient in the treatment of cluster headache<sup>6</sup>.

Results of our study showed gabapentin to be effective as prophylactic treatment of cluster headache in patients refractory to previous prophylactic therapy. We observed a significant reduction in headache frequency, intensity and medication use during the follow up period. The high efficacy rates observed in our study might be promising, since not many prophylactic medications are available for the treatment of this debilitating condition. We compared our results with other trials that evaluated the efficacy of gabapentin in cluster prophylaxis.

In a case report of episodic cluster headache, gabapentin 300 mg twice daily proved efficient, with a transient side effect (drowsiness)<sup>7</sup>. Another case report of chronic cluster headache describes response to gabapentin at a dose of 1800 mg, with the patient being symptom-free<sup>8</sup>. In an open-label study, 8 episodic and 4 chronic cluster patients previously refractory to other prophylactic therapy were treated with gabapentin 300 mg three times daily; all patients were pain-free within 8 days of treatment introduction<sup>9</sup>. In patients with episodic cluster headache, therapy was discontinued after 2 months and no relapse occurred during 3 months of follow up; in chronic cluster patients no new attacks were reported during 4-month follow up; only two patients reported mild drowsiness as an adverse event<sup>9</sup>. Gabapentin was also found to be efficient in patients with chronic cluster headache; 6 of 8 patients refractory to first-line treatment responded to this therapy<sup>10</sup>.

In three open-label trials, divalproex sodium and sodium valproate were found to be efficient in reduction of headache frequency; in one trial, 9 of 15 patients

reported complete remission of cluster headaches<sup>11-13</sup>. However, a double-blind placebo-controlled study in 96 patients turned out to be unfavorable: a reduction by at least 50% in the mean number of attacks *per week* was observed in the sodium valproate group and by as much as 62% in the placebo group<sup>14</sup>.

In six open label studies with small series of patients, topiramate was efficient in reducing the frequency of attacks and high percentage of remission was reported in most of these studies; the response occurred within 1-3 weeks<sup>6</sup>. Topiramate, 25-100 mg in 1-2 divided doses during the cluster period and 2 weeks thereafter, reduced cluster attacks in 19 of 27 patients within 3-14 days<sup>15</sup>.

In our study, a significant reduction was recorded in the number of days with headache and headache intensity, i.e. by 12 headache days/4 weeks or 44.94% reduction in headache frequency; our results are similar to a study with gabapentin<sup>9</sup>, and to studies with divalproex sodium<sup>12,13</sup> and topiramate<sup>15</sup>.

The shortcomings of our study were the small number of patients included and study design, as it was not a placebo-controlled double-blind study. However, it is unlikely that the results were due to placebo effect, since prior trials of preventive medications had failed in most of our patients. In our study, gabapentin treatment of patients with cluster headache at daily doses of 900-2400 mg resulted in a significant mean reduction of migraine days, reduction in pain intensity and in the use of acute medications. Although adverse events occurred in a relatively high percentage, the treatment with gabapentin was safe and well tolerated in the majority of patients. Our findings warrant further trials, in a larger number of patients, preferably as double-blind placebo-controlled studies. However, we hope that the results of our study will help other clinicians in the treatment of cluster patients unresponsive to usual prophylactic treatment.

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#### Sažetak

#### GABAPENTIN U PROFILAKSI KLUSTER GLAVOBOLJE: OPSERVACIJSKA OTVORENA STUDIJA

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Kluster glavobolja je izrazito bolni sindrom koji se češće javlja kod muškaraca. Premda se u većini slučajeva javlja periodično, kluster glavobolja ima značajan utjecaj na kvalitetu života bolesnika. Akutna terapija najčešće nije dovoljna te je većini bolesnika potrebna i profilaktična terapija. Cilj ove studije bio je procijeniti učinkovitost i sigurnost gabapentina u profilaksi kluster glavobolje kod bolesnika koji su prethodno uspješno ili neuspješno liječeni drugim profilaktičnim lijekovima. Studija je uključivala 14 bolesnika, 9 muškaraca i 5 žena (prosječne dobi 42±15 godina). Gabapentin se postupno uvodio u terapiju; doza održavanja je bila od 900-2400 mg: 900 mg u 6, 1200 mg u 2, 1800 mg u 4 i 2400 mg na dan u 2 bolesnika. Prosječno trajanje liječenja je bilo 3,5 mjeseci (raspon 2-5 mjeseci). Unutar 1-2 tjedna bolesnici su naveli poboljšanje uz terapiju. Prosječni broj dana s glavoboljom/4 tjedna bio je smanjen s 378 (srednja vrijednost 27) na početku terapije na 210 (srednja vrijednost 15) na kraju razdoblja praćenja, što je smanjenje za 12 dana s glavoboljom /4 tjedna (44,94%). Intenzitet boli bio je smanjen za 25% kod 1 (7,14%) bolesnika, za 50% kod 8 (57,14%), za 75% kod 3 (21,4%) bolesnika, a 2 (14,28%) bolesnika uopće nisu naveli poboljšanje. Nuspojave je prijavilo 8/14 (57,14%) bolesnika i uglavnom su bile blagog ili umjerenog intenziteta. Najčešće prijavljene nuspojave bile su pospanost, omaglica, usporenost i konstipacija. Niti jedan bolesnik nije prekinuo studiju zbog nuspojava.

**Ključne riječi:** Kluster glavobolja – terapija lijekovima; Kluster glavobolja – prevencija i kontrola; Octena kiselina – terapijska primjena; Analgetik – terapijska primjena; Migrena – terapija lijekovima