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Chronic migraine prevention with topiramate

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Abstract Chronic migraine (CM) is a disabling condition with not many treatment strategies available. Topiramate is effective in episodic migraine prevention, however little is known about its effect in CM. An open label study was performed. Sixty-four patients diagnosed with CM or probable CM according to the IHS diagnostic criteria were enrolled, 50 patients were available for analysis and an intention-to-treat methodology was applied. The primary endpoint considered was the number of patients with a decrease in headache frequency higher than 50%. The median dose was 100 mg, a reduction in frequency higher than 50% occurred in 33 patients (66%) and 14 (28%) presented a complete response, defined as a frequency reduction higher than 95%. The medication was well tolerated. The most common side effects found were weight loss, paraesthesias, nausea, cognitive dysfunction, fatigue, somnolence, insomnia and depression. Our findings suggest that topiramate is effective in CM prophylaxis.

Key words Chronic migraine • Prevention • Antiepileptic drugs • Topiramate

Introduction

Migraine is a common and debilitating disorder with a 1-year prevalence of approximately 18% in women and 6% in men [1]. Chronic migraine (CM) is even more incapacitating; it is prevalent in the general population, affecting 2%–3% of individuals [2]. CM has been recently added to the new International Headache Society (IHS) classification system [3]. It is one of the most frequent conditions found in headache centres, but, to date, there is still no satisfactory therapeutic approach for these patients.

The major medication groups for the preventive treatment of migraine include beta-adrenergic blockers, antidepressants, calcium channel antagonists, serotonin antagonists, anti-convulsants, non-steroidal anti-inflammatory drugs (NSAIDs) and others (including riboflavin, minerals and herbs).

Neuromodulators have been increasingly recommended for migraine prevention because of placebo-controlled, double-blind trials that prove it to be effective. Topiramate has been proven effective for episodic migraine prevention, but little is known about the efficacy of topiramate in CM preventive treatment. We did a study to evaluate the role of topiramate in CM.

Methods

Sixty-four patients diagnosed with chronic migraine or probable chronic migraine according to the IHS diagnostic criteria [3]

were enrolled. Exclusion criteria were carbonic anhydrase (CA) inhibitors, history of renal calculi, pregnancy or lactation. Patients with neurological diseases or taking any prophylactic treatment for headache at the time of our observation were also excluded. Fourteen patients dropped out of the study because they were lost to follow-up (8 patients) or had adverse events (somnolence in 2, cognitive dysfunction in 2, epigastralgia 1, depression 1). The patients were lost to follow-up because: moved to another state (1), denied pharmacological treatment, not because of side effects (2), gave up participating in a clinical trial (5). Fifty patients (40 women, 10 men) were evaluated by the intention-to-treat methodology. The primary endpoint considered was the number of patients with a decrease in headache frequency higher than 50%. All patients received topiramate 25–200 mg, mean dose of 91 mg, median dose 100 mg. A titration schedule was provided over the first month, with follow-ups every 4 weeks for 12 weeks. The headache diaries were collected and data on headache frequency, intensity, duration and analgesic consumption were evaluated. All patients gave their informed consent to participate. The study was approved by the Local Ethics Committee.

One-way repeated measures analysis of variance was used to compare values between the four time periods. Tukey's method was used for post hoc pairwise comparisons. The Fisher and chi-square tests were applied for 2x2 analysis. All *p*-values reported were two-tailed and values lower than 0.05 were considered significant.

Results

The mean age was 41.4±11.7 years. Body mass index (BMI) mean was 24.7. Thirty-one patients had normal BMIs, 12 patients were overweight and 7 had a BMI higher than 30. Thirty-nine patients presented a history of acute medication overuse, 32 with simple/combination analgesics, 9 with triptans, 8 ergotamines and 3 NSAIDs. The mean history of headaches was 20.5 years, and the mean history of daily headaches was 4.7 years.

The primary endpoint, headache response higher than 50% in frequency reduction, was achieved by 33 patients (66%). Eight (16%) patients did not respond and 9 (18%) had a less than 50% reduction. Fourteen (28%) presented a complete response, defined as a frequency reduction higher than 95%. No difference was found in response in patients with or without acute medication. Twenty-five patients who responded and 14 non-responders were overusers (p=NS).

Frequency, duration and intensity were significantly reduced (p<0.001) when comparing the first to the last month of treatment. Results were already significant as early as the first month. The mean weight loss found was 1.654 g, 2.75% of the body weight; 20% of the patients lost more than 5% of body weight. The most common side effects encountered were weight loss (in 38 patients, 76%), paraesthesias (24, 48%), nausea (6, 12%), cognitive dysfunction (5, 10%), fatigue (4, 8%), somnolence (3, 6%), insomnia (2, 4%) and depression (2, 4%).

Discussion

In this open study we found a favourable response in headache frequency, intensity and duration of CM patients treated with topiramate. The side effect profile showed topiramate to be a tolerable drug in CM patients. One important finding is that headache response occurred already in the first month of treatment. Another relevant issue is that no significant difference in headache response was found when patients with a history of acute medication overuse (although not fulfilling the criteria for medication overuse headache) were compared to those with pure chronic migraine.

Topiramate has been studied for migraine prevention in large, placebo-controlled clinical trials. Topiramate was superior to placebo as measured by reduction in monthly migraine frequency, overall 50% responder rate, reduction in monthly migraine days and reduction in the rate of daily rescue medication use in all trials [4–6]. The target dose appeared to be 100 mg.

Although there is published data available from recent studies with large numbers of patients included, long observation periods and good methodology, the most critical patient group for the clinician in a tertiary headache centre, chronic migraineurs, has not been properly investigated. Silvestrini et al. [7] showed the efficacy of topiramate in chronic migraine with analgesic overuse preventive treatment. Only 28 patients were studied receiving topiramate in a lower dose (50 mg). A significantly lower 28-day headache frequency in comparison to those treated with placebo was observed.

Our study shows that topiramate in a median dose of 100 mg is effective and well tolerated in chronic migraine prevention. We decided to include both acute medication overuse patients and non-overusers in our study, because the sample population would be closer to the clinical profile found in headache centres, therefore the results express a more real clinical scenario. Placebo-controlled trials are required for a better understanding of the clinical response of chronic migraine with topiramate preventive treatment.

Pathophysiological considerations suggest that the possible basis for the shift from episodic to chronic headache can be progressive damage to the central nociceptive system [8]. The anti-convulsant activity of most anti-epileptic drugs is thought to be due to a state-dependent blockade of voltage-dependent Na^+ or Ca^{2+} chan-

nels, or an ability to enhance the activity of GABA at $GABA_A$ receptors. Topiramate can influence the activity of some types of voltage-activated Na^+ and Ca^{2+} channels, $GABA_A$ receptors and the alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate subtype of glutamate receptors. Topiramate also inhibits some isozymes of CA and exhibits selectivity for CA II and CA IV [9].

We have recently shown that chronic migraine is related to a hyperglutamatergic state in the brain, confirmed by higher cerebrospinal fluid glutamate levels in chronic migraineurs compared to controls [10]. Therefore, topiramate may be a candidate for chronic migraine prevention.

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