Introduction

Chronic daily headache (CDH), defined as 15 or more headache days per month [1], may severely affect the quality of life of the patients, impairing their work and non-work activities and reducing their productivity [2]. Among these patients, those who are refractory to treatment are left with a debilitating headache disorder and constitute the most challenging population in a headache clinic.

Antiepileptic drugs play an important role in the treatment of headache disorders [3] and other pain syndromes [4–6]. Topiramate, a new generation broad-spectrum anticonvulsant, has recently been tried as a preventive drug in the treatment of various headache syndromes. These studies show that topiramate may have a place in the prevention of migraine [7–10], transformed migraine [7] and cluster headache [7, 11].

We hereby report on our experience with topiramate, shown to have possible significant adverse events (e.g., somnolence, paraesthesias and cognitive deficits), in the treatment of patients with CDH who were refractory to multiple previous treatments.

Methods

We included patients with CDH who were refractory to treatment trials with multiple modalities such as valproic acid, tri-
cyclic antidepressants, serotonin specific reuptake inhibitors, non-steroidal anti-inflammatory drugs, analgesics, greater occipital nerve blocks and acupuncture, homeopathic or herbal treatments (used by some of the patients). We included males or females older than 18 years in whom the CDH was not due to medication overuse. The patients had an ophthalmological examination prior to the treatment and their weight was monitored. Data was collected through daily headache diaries. To improve tolerability, we started topiramate at a daily dose of 12.5 mg and increased the dosage biweekly by 12.5 mg, given bid. Weekly increments were further used if no adverse events were noted.

The Institutional Review Board approved the study according to the Helsinki rules and informed consent was obtained from each subject.

**Results**

Eleven patients with refractory CDH were treated with topiramate. The average age of the patients was 51±13 years (64% women). The median duration of the CDH at the time of the study entry was 5 years (range 2–25 years). Five patients had CDH of transformed migraine type. The rest had CDH of tension-type headache; among them one patient had recurrent surgeries for CSF shunting (initially performed for the treatment of hydrocephalus) and 2 patients had headache related to a post-traumatic stress disorder (Table 1).

Topiramate successfully relieved headaches in 7 patients (64%). The number of headache days per week decreased by 66% (median; range 0%–96%); the headache hours per day were reduced by 50% (median; range 0–90%) and the severity of the headache lessened by 50% (median; range 0%–79%). In the 7 responders to topiramate the weekly analgesic consumption decreased by 74%±22% (average, range 50%–100%) (Table 2). These effects continued for an average follow-up of 8±4 months (range 5–14 months).

Initial headache relief was noted after 5±4 weeks of treatment. The maximal daily dose of topiramate used by the patients who had headache relief was 100 mg (median; range 25–250 mg) (Table 2). The 4 patients with no headache relief discontinued the treatment due to adverse effects (patients 10, 11; Table 2) or due to lack of efficacy (2 patients). The analgesic consumption of these patients did not change during the study follow-up.

Mild and tolerable adverse events of topiramate were reported by 7 patients (64%) and consisted of tiredness (2 patients), acral paraesthesias (2 patients) and difficulty in concentrating (2 patients) (Table 2). Weight loss and weight gain (3 kg) were noted in 2 patients.

**Discussion**

In this study we found that topiramate was an effective treatment for patients with refractory CDH. Of these patients, considered as ‘treatment unresponsive’, 7 patients (64%) gained with topiramate a significant reduction in the headache frequency, severity and analgesic consumption.

Patients with CDH do respond somewhat to various medical treatments and therefore the available population was limited, but represented the most challenging population in a headache clinic. Although this was an open

| Patient no. | Gender | Age, years | CDH type | CDH duration, years |
|-------------|--------|------------|----------|---------------------|
| 1           | F      | 55         | Tr. Mig. | 2                   |
| 2           | F      | 63         | Tr. Mig. | 6                   |
| 3           | F      | 57         | Tr. Mig. | 2                   |
| 4           | M      | 23         | TTH*     | 4                   |
| 5           | F      | 54         | Tr. Mig. | 5                   |
| 6           | F      | 69         | TTH      | 15                  |
| 7           | M      | 49         | TTH*     | 10                  |
| 8           | F      | 46         | TTH      | 5                   |
| 9           | F      | 49         | Tr. Mig. | 4                   |
| 10          | M      | 58         | TTH      | 25                  |
| 11          | M      | 34         | TTH**    | 10                  |

Tr. Mig., transformed migraine; TTH, tension-type headache

*Patient diagnosed with post-traumatic stress disorder

**Patient had shunt insertion for the treatment of hydrocephalus
uncontrolled study of a small population, the effect of the treatment that continued for 8±4 months is much longer than that expected for placebo. We therefore assume that it represents, in these particular our patients, a true effect of the treatment. Our results are in accordance with early observations on the usefulness of topiramate in transformed migraine [7] and we show here that the drug may be effectively used for other types of CDH.

We increased the dose of topiramate gradually in small increments. Although there were some adverse events, we assume that this modality of drug augmentation enabled the high tolerability of topiramate during the long follow-up.

Conclusions

We found topiramate to be an effective, long-lasting preventive treatment option for patients with refractory CDH. Small increments of the dosage over many weeks contributed to high tolerability of the drug.

References

1. Silberstein SD, Lipton RB, Sliwinski M (1996) Classification of daily and near-daily headaches: field of revised IHS criteria. Neurology 47:871–875
2. D’Amico D, Usai S, Grazzi L, Rigamonti A, Solari A, Leone M, Bussone G (2003) Quality of life and disability in primary chronic daily headaches. Neurol Sci 24[Suppl 2]:S97–S100
3. Silberstein SD (1996) Divalproex sodium in headache: literature review and clinical guidelines. Headache 36:547–555
4. Lunardi G, Leandri M, Albano C, Cultrera S, Fracassi M, Rubino V, Favale E (1997) Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. Neurology 48:1714–1717
5. Novelli GP, Trovati F (1998) Gabapentin and neuropathic pain. Pain Clin 11:5–32
6. Thomson T, Bertilsson L (1984) Potent therapeutic effect of carbamazepine 10,11-epoxide in trigeminal neuralgia. Arch Neurol 41:598–601
7. Mathew NT, Kailasam J, Meadors L (2002) Prophylaxis of migraine, transformed migraine, and cluster headache with topiramate. Headache 42:796–803
8. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, Neto W, Schwabe S, Jacobs D; MIGR-002 Study Group (2004) Topiramate for migraine prevention: a randomized controlled trial. JAMA 291:965–973
9. Silberstein SD, Neto W, Schmitt J, Jacobs D; MIGR-001 Study Group (2004) Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol 61:490–495
10. Diener HC, Tfelt-Hansen P, Dahlof C, Lainez MJ, Sandrini G, Wang SJ, Neto W, Vijapurkar U, Doyle A, Jacobs D; MIGR-003 Study Group (2004) Topiramate in migraine prophylaxis – results from a placebo-controlled trial with propranolol as an active control. J Neurol 251:943–950
11. Wheeler SD, Carrazana EJ (1999) Topiramate treated cluster headache. Neurology 53:234–236