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Topiramate for patients with refractory migraine: an observational, multicenter study in Spain

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Introduction: The efficacy of current preventive migraine treatments is limited. In addition, tolerability problems are not infrequent.

Objectives: To check our experience with topiramate in the treatment of patients with refractory migraine.

Patients and methods: We offered treatment with topiramate to patients with the diagnosis of International Headache Society (IHS) migraine who had not responded to or tolerated beta-blockers, amitriptyline, flunarizine and/or valproate. This series is made up of 115 patients (88 women), between 16 and 81 years. Most of them (n = 79) fulfilled the Silberstein et al. criteria for transformed migraine. The parameters analyzed were «response» (reduction in migraine frequency > 50 %), excellent response (> 75 %) and tolerability.

Results: After 3 months, the maintenance doses of topiramate ranged from 25 to 400 mg, though most patients took 100 mg. Twenty-four (21 %) patients withdrew due to adverse events, mostly cognitive difficulties, that had already occurred with doses as low as 25-50 mg, while 26 (23%) found topiramate ineffective. The remaining 65 (56%) patients responded, 34 with excellent response. Sixteen patients (10 obese) lost weight (3-13 kg).

Conclusions: Topiramate seems to be a good therapeutic option for about half of the patients with refractory migraine. In these patients response is usually excellent. Intolerance due to adverse events appears in one-fifth of the cases early and at low doses.

Key words:
Migraine. Migraine prevention. Topiramate

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Topiramato para pacientes con migraña refractaria: estudio multicéntrico observacional en España

Introducción: La eficacia de los tratamientos preventivos antimigraña es limitada. No son, además, infrecuentes los efectos adversos.

Objetivos: Explorar nuestra experiencia en el tratamiento con topiramato de pacientes con migraña refractaria.

Pacientes y métodos: Se ofreció tratamiento con topiramato a pacientes con el diagnóstico de migraña según la International Headache Society (IHS) que no hubieran respondido o tolerado beta-bloqueantes, amitriptilina, flunarizina y/o valproato. Esta serie comprende un total de 115 pacientes (88 mujeres), de entre 16 y 81 años de edad. La mayoría (n = 79) cumplían los criterios de Silberstein et al. para el diagnóstico de migraña transformada. Los parámetros evaluados fueron «respuesta» (reducción en frecuencia de las crisis > 50 %), respuesta excelente (> 75 %) y tolerabilidad.

Resultados: Tras 3 meses de tratamiento las dosis de mantenimiento de topiramato oscilaron entre 25 y 400 mg, si bien la mayoría de los pacientes tomaban 100 mg. Un total de 24 pacientes (21 %) hubo de abandonar el tratamiento por efectos adversos, en la mayoría de los casos cognitivos, ya desde el inicio del tratamiento y a dosis bajas, mientras que 26 (23 %) no respondieron. Los 65 pacientes restantes (56 %) respondieron, 34 de ellos con respuesta excelente. Un total de 16 pacientes (10 eran obesos) perdieron peso (3-13 kg).

Conclusiones: El topiramato es una buena opción de tratamiento para aproximadamente la mitad de los pacientes con migraña refractaria. En estos pacientes, la respuesta suele ser excelente. La intolerancia por efectos adversos aparece en uno de cada 5 pacientes al inicio del tratamiento, ya con dosis bajas.

Palabras clave:
Migraña. Tratamiento preventivo. Topiramato

INTRODUCTION

Migraine is a frequent condition affecting 18 % of women and 6 % of men. The American Migraine Study reported

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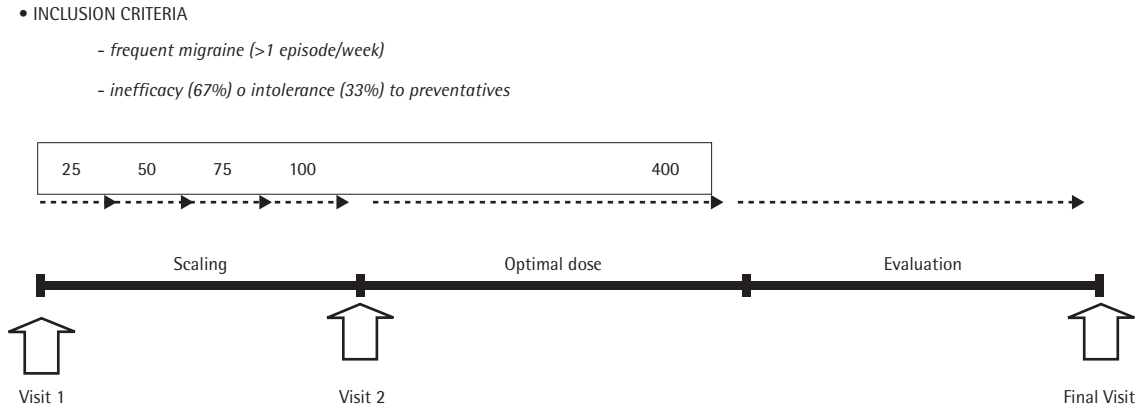

Figure 1 *Summary of study methodology (total duration 3 months).*

that 24 % of migraine sufferers experience four or more migraine attacks every month. However, only 3 to 5 % of migraine sufferers receive preventive therapy[1]. Classes of agents used as preventatives for migraine include beta-blockers, calcium-channel blockers, serotonin antagonists, antidepressants, non-steroidal anti-inflammatory drugs, and antiepileptics. Many patients with migraine find the currently available preventatives unsatisfactory, due to their limited efficacy and not infrequent adverse effects. Consequently, there is a need for better prophylactic options[2].

Several recent open-label or small placebo-controlled studies suggest that topiramate may be efficacious for prophylaxis of migraine and cluster headache[3-11]. Topiramate has a variety of mechanisms of action that could potentially contribute to migraine prophylaxis, including state-dependent inhibition of voltage-gated Na^+ and Ca^{++} channels, inhibition of glutamate-mediated neurotransmission at the AMPA/kainate receptor subtypes, and enhancement of GABA receptor-mediated chloride flux[12].

We report here our experience with topiramate in the prophylaxis of patients with frequent migraine previously refractory to usual preventatives.

METHODS

We offered treatment with topiramate to patients with the diagnosis of frequent IHS migraine[13] who had not tolerated (33 %) or responded (67 %) to beta-blockers, amitriptyline, flunarizine and/or valproate. Even though each investigator was free to use his own treatment protocol in a particular patient, topiramate was usually initiated at 25 mg per day and was increased by 25 mg weekly up to a target dose of 100 mg/day. Two obligatory follow-up visits were scheduled. The first one took place at the end of the initial treatment month. This visit was planned mainly to check for tolerability and to increase topiramate dose if no response had occurred. Maintenance dose could be even lower if tolerability problems appeared, or else increased up to a maximum of 400 mg daily, if migraine frequency did not improve. The final obligatory visit took place at the end of the third treatment month. In this visit, headache frequency in the last month was rated upon a calendar review when available, or based on patient recall when a calendar was not available (fig. 1). The parameters analysed in this visit were «response» (reduction in migraine frequency > 50 %), excellent response (> 75 %) and tolerability.

RESULTS

Patients

This series includes a total of 115 patients (88 women), aged between 16 and 81 years (mean 43 years). Ninety-six met migraine without aura criteria, while the remainder had a history of both migraine with aura and migraine without aura episodes. All the patients had frequent (>1 migraine days per week) migraine episodes. In fact, 79 met Silberstein et al's criteria for transformed migraine[14]. After 3

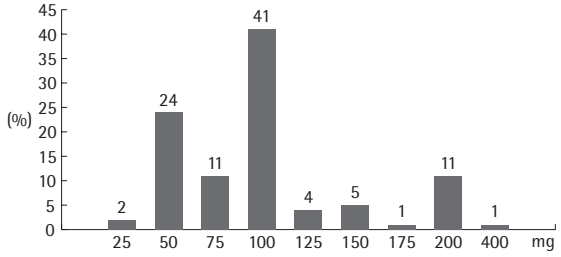

Figure 2 *Distribution of topiramate doses among the patients included in this study.*

months, daily maintenance doses of topiramate varied between 25 and 400 mg (mean 98.7 mg per day; mode and median 100 mg per day). The distribution of topiramate doses in this study is illustrated in figure 2.

Efficacy

A total of 26 patients (23 %) found topiramate inefficacious. Conversely, 65 patients (56 %) showed response to topiramate therapy. Response was excellent in 34 cases (fig. 3).

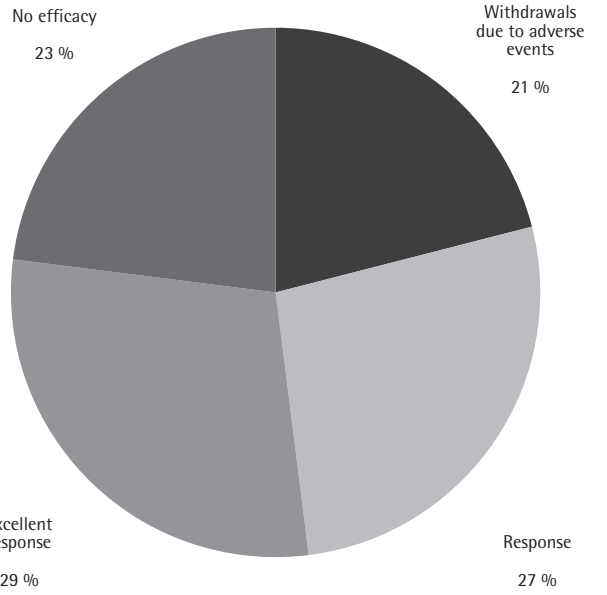

Figure 3 *Summary of study results.*

Tolerability

Twenty-four (21 %) patients withdrew due to adverse events, already at doses as low as 25-50 mg and most of them during the first month of therapy. One of these withdrawals was due to excessive weight loss (13 kg), one due to digestive intolerance and the remaining 22 due to cognitive difficulties (expressed as decreased concentration or memory problems) sometimes associated with drowsiness sensation. The remaining 91 patients frequently reported other adverse events (being the most frequent distal paresthesias in at least 34 cases), but they were mild, well tolerated and improved on decreasing the dose of topiramate (fig. 4). No serious adverse events were seen. Sixteen patients (10 obese) referred to significant weight lost (3-13 kg in 3 months).

CONCLUSIONS

The results of this observational study indicate that topiramate is a good therapeutic option to try in migraine patients refractory to other preventatives and/or frequent attacks. In a specialist's clinical setting, topiramate seems to be effective in about half of these patients. The response was usually excellent in these patients, which, together with the previous failure to other preventatives also administered by us, make a relevant placebo effect very unlikely. Our findings concur with those reported in placebo-controlled trials and observational studies[3-11]. Edwards et al, in a placebo-controlled trial of episodic migraine, found a 50 % or greater reduction in headache frequency in 47 % of patients. Storey et al, in a placebo-controlled trial of episodic migraine patients, reported a median percent reduction in monthly headaches of 33 %. Several authors have recently studied the effect of topiramate in both episodic and transformed migraine in observational trials. Response in transformed migraine patients in these studies has ranged from

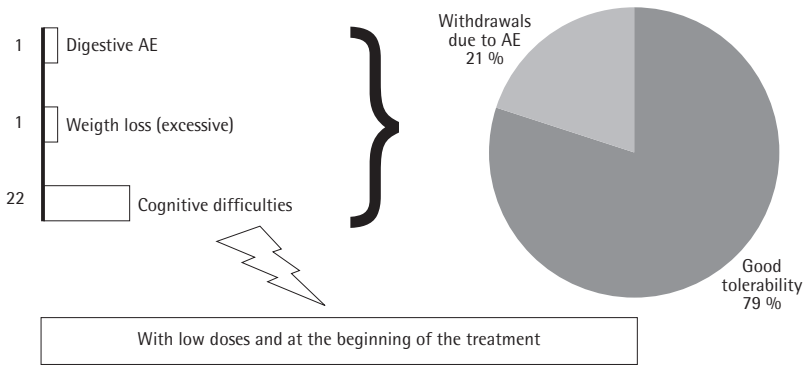

Figure 4 *Tolerability of topiramate.*

30 to 58 % of patients. The rather high efficacy rates in our observational study may be due to the ability to optimize the dose and individualize treatment, and could be representative of the outcomes which might be expected in a real clinical setting.

The data of our study might help to clarify two debatable points: what the best dose of topiramate should be and what the adverse event profile of topiramate is in migraine patients. In our experience, and concurring with that of Mathew et al.[10], the optimal dose of this drug for migraine prevention in most patients is around 100 mg/day. Higher doses lead to an increase in efficacy in few patients and clearly impair tolerability[12]. Poor tolerability was the reason for discontinuing topiramate in exactly 21 % of our patients. Adverse events were mostly subjective cognitive impairment and, very importantly, usually appeared already on doses as low as 25-50 mg daily. It should, therefore, be clearly explained to the patients when prescribing this drug.

Similarly to other trials in headache and non-headache patients, weight loss was a quite frequent adverse event[11,15]. The reported range of weight loss is consistent with that of previous studies. With only one exception, it was not considered by our patients as a negative adverse event. In fact, most considered weight loss as a beneficial adverse event. In summary this observational study provides further experience with topiramate in migraine prophylaxis, in a large series of ambulatory patients. The results of the large controlled trials of topiramate in this setting are awaited for a confirmation of its efficacy.

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