Original article

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Topiramate and temporal lobe epilepsy: an open-label study

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ABSTRACT – *Purpose*. To evaluate the efficacy and tolerability of topiramate (TPM) as monotherapy for patients with temporal lobe epileptic seizures based on an observational study. *Methods*. We evaluated 41 patients (20 female, mean age 54+18 years) with temporal lobe epilepsy (TLE) referred to the Epilepsy Unit, University of Catanzaro, Italy. Patients received TPM as monotherapy directly or after having taken other antiepileptic drugs. Seizure frequency changes and adverse events were recorded. Follow-up was conducted for a period of at least two years after treatment. *Results*. Patients received TPM, 50-600 mg/day, *de novo* (*n*=29) or initially as add-on therapy before the switch (*n*=12). In total, 28 of 41 patients achieved seizure freedom, whereas 10 showed a ≥50% reduction of seizure frequency. Two patients did not respond well and one patient discontinued TPM due to adverse effects. *Conclusions*. Our results confirm that TPM as either monotherapy or add-on therapy at doses of 50-600 mg/day effectively reduces seizure frequency in TLE. TPM is particular effective and very well tolerated in patients with mild TLE.

Key words: topiramate, temporal lobe epilepsy, antiepileptic drugs

Topiramate (TPM) is derived from D-fructose, initially used as an antidiabetic drug. It is a novel antiepileptic drug (AED) having been shown to have striking antiepileptic action in animal models (Park *et al*., 2008). The use of these models indicated that TPM exerts multiple actions such as an inhibitory effect on sodium conductance, increasing GABA-mediated chloride influx into neurons, and antagonism of amino-3-hydroxy-5-methyl-4-isoxazole propionic acid AMPA/kainate glutamate receptor (Kaminski *et al*., 2004; Herrero *et al*., 2002; Jette *et al*., 2008). Several clinical trials of TPM as adjunctive therapy with standard AEDs have demonstrated that TPM has a broad spectrum of actions, effective against partial-onset seizures (Giannakodimos *et al*. 2005; Jette *et al*., 2008), primary generalised tonic-clonic seizures (Bergey, 2005), and seizures associated with Lennox-Gastaut syndrome (Glauser *et al*., 2000). The excellent results of TPM as adjunctive therapy for patients with refractory epilepsy, mainly with temporal lobe epilepsy (TLE), suggested that this drug could also be used as monotherapy. For TLE, the efficacy of TPM as monotherapy, as for many other AEDs, has only been evaluated in adults with

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chronic, refractory partial-onset seizures (Sachdeo *et al*., 1997), despite some forms of epilepsy having a mild course. Recent studies described clinical features and outcome of TLE patients who had a benign form of TLE (bTLE) (Aguglia *et al*., 1998; Gambardella *et al*., 2003; Labate *et al*., 2011). Furthermore, MRI evidence of hippocampal sclerosis (HS) in about 40% of these patients with bTLE has pointed out that the presence of HS itself does not necessarily indicate intractable epilepsy with a worse outcome as previously thought (Labate *et al*., 2006; Labate *et al*., 2008; Labate *et al*., 2011).

To evaluate the efficacy of TPM in a population of TLE patients with mild and refractory partial epilepsy, we conducted an observational open-label study in adults and children taking TPM as monotherapy or as a second AED choice due to inefficacy of the first AED.

Patients and methods

This open-label study was conducted at an epilepsy outpatient clinic at the University of Catanzaro from June 2009. Patients were eligible for the study if they were at least three years of age. The study group consisted of 41 consecutive patients (20 females; mean age: 54+18 years) referred to our clinic and recruited prospectively. The study was approved by the University Hospital Ethics Committee and all subjects and their guardians, in the case of children, gave informed consent to participate. For all patients, the diagnosis of epilepsy was based on the International Classification of Epilepsies (Commission, 1989). The following features were noted: sex, age, history of migraine, seizure type, AEDs used prior to TPM, age at epilepsy onset, seizure frequency, abnormal physical and neurological examination, family history of epilepsy or febrile convulsions (FC), and laboratory and neuroimaging findings. Seizure types were identified according to the classification of epileptic seizures and syndromes by the International League Against Epilepsy (Commission, 1989). The diagnosis of TLE was made on the basis of a constellation of clinical, EEG, and MRI criteria which are considered to be reliable interictal indicators of TLE (Commission, 1989). The diagnosis of TLE was mainly based on typical temporal auras or interictal EEG discharges, maximum over the temporal lobes. Any suggestion of seizure onset outside the mesial temporal structures by semiology or EEG findings was an exclusion criterion. All patients underwent several interictal EEGs including routine EEGs while awake and asleep. The interictal EEGs were recorded according to the 10-20 international system with supplementary T1 and T2 electrodes (Gambardella *et al*., 1998). The EEG abnormalities (spikes, spike waves, and runs of sharp theta/delta waves of temporal intermittent rhythmic delta activity over one temporal region) were labelled as unilateral if confined to one temporal side at least 95% of the time. All patients had a conventional MRI (1.5 Tesla) examination, based on a protocol routinely used for patients with epilepsy (Labate *et al*., 2006), including T2-weighted images, and a coronal 3D sequence with contiguous slices, with and without administration of gadolinium. Exclusion criteria were: extratemporal epilepsies, generalised epilepsies, status epilepticus, epilepsia partialis continua, non-epileptic seizures, clinically significant laboratory abnormalities, nephrolithiasis, mental retardation, poor compliance, pregnancy, alcohol or drug abuse within the past years, hypersensitivity to carbonic anhydrase inhibitors or sulfonamides, and suicide attempt or psychiatric disorder requiring therapy. Each patient received a starting dose of 12.5 mg TPM nightly for a week and a following increment to at least 50 mg/day over four weeks, while withdrawl of any anticonvulsant being used previously without efficacy was initiated.

Patients were clinically observed every three months during a follow-up of more than two years. Firstly, the efficacy was assessed by measuring changes in seizure frequency and secondly, side effects and tolerability were observed. We classified patients after treatment into four categories: seizure freedom, $\geq$50% seizure reduction; <50% seizure reduction, and those that withdrew from the trial. Diagnosis, treatment decision and grading the efficacy were made by a single trained neurologist with special expertise in epilepsy (AL).

Categorical variables were reported as counts and percentage. Frequency distributions among patient groups were compared using the χ^2 test and Monte Carlo or Fisher exact test, as appropriate, when the expected frequencies were low. The unpaired t-test was used to evaluate differences in mean of continuous variables among groups. Statistical analysis was performed using the Statistical Package for Social Science software (SPSS, version 17.0, Chicago, IL) for Windows.

Results

Clinical characteristics of patients are summarised in *table 1*. In detail, 29 (70%) of 41 subjects had benign TLE with very mild epilepsy (bTLE), *i.e*. seizure-free patients or patients with either occasional auras or not more than two disabling (complex partial or secondary generalised) seizures per year for at least two following years. The remaining 12 subjects had symptomatic epilepsy (sTLE); four of these patients had HS, four patients had vascular lesions, two patients had a brain tumour, and three had post-traumatic gliosis. The diagnosis of both bTLE and sTLE was made before starting

Table 1. Features in patients with bTLE or sTLE.

Clinical Features	bTLE (*n*=29)	sTLE (*n*=12)
Age (Mean±SD)	57±17	52±19
Age at onset (Mean±SD)	48±18,7	34,7±21,3
Sex (n, %)		
Male	13	8
Female	16	4
Familial history of epilepsy (n,%)	5 (17)	3 (25)
Febrile convulsions (n,%)	1 (3,4)	1 (8,3)
Mean dose of TPM (mg/day)	197±13	379±13
EEG (n, %)		
Normal	8	0
Left spikes or/and sharp waves	7	7
Right spikes or/and sharp waves	11	2
Bilateral spikes or/and sharp waves	3	3
Previous drugs (n, %)		
Carbamazepine		6
Clobazam		2
Lamotrigine		2
Fenobarbital		2
None	29	

bTLE benign temporal lobe epilepsy; sTLE: symptomatic temporal lobe epilepsy; TPM: topiramate.

TPM treatment. The vast majority (36 patients, 87%) reported a history of migraine.

All patients with bTLE (70%) received TPM as *de novo* monotherapy while 12 with sTLE received TPM initially as add-on therapy to other drugs (carbamazepine, lamotrigine, and valproate) before the switch. The mean dose of TPM achieved was 250±109 mg. As shown in *figure 1*, seizure frequency was dramatically reduced for the great majority of our population (93%). Of 41 patients, 28 (93%; 19 with bTLE and nine with sTLE) reached seizure freedom. Ten patients (25%; seven with bTLE and three with sTLE) showed reduction in seizure frequency by more than 50%. Only two subjects had an unsatisfactory response with less than 50% reduction of seizures. One patient dropped out from the study because of side effects (excessive somnolence), and a gradual and not excessive decrease (average of 2 kilograms) in body weight occurred during TPM therapy in four patients. Some patients (three with bTLE) during the follow-up spontaneously reduced the dose of TPM because of very rare simple partial auras (one per year). Between the two groups, we did not observe statistical difference

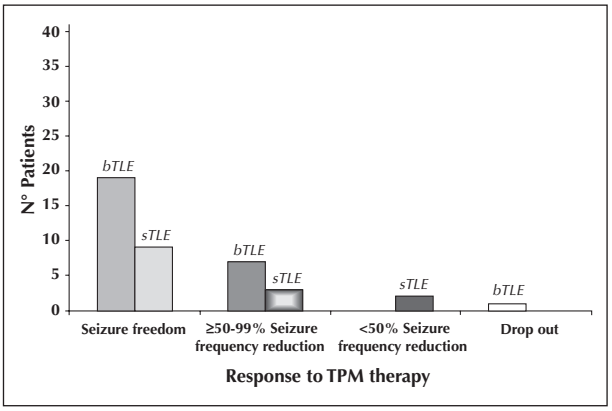

Figure 1. Overall response to TPM treatment in patients with bTLE and sTLE.

between sex (p=0.240), age at onset (p=0.097), and family history of epilepsy (p=0.240).

No changes on interictal EEGs were observed during the follow-up.

Discussion

To our knowledge, this is the first open-label study that reports on the efficacy and safety of TPM as monotherapy for the treatment of temporal lobe epileptic patients regardless of their seizure frequency.

TPM has been extensively reported to be effective as add-on therapy for refractory partial epilepsy in several placebo-controlled studies (Sachdeo *et al*., 1997; Giannakodimos *et al*., 2005; Jette *et al*., 2008). However, we have recently showed that many patients with TLE have a benign evolution and very good response to AEDs, regardless of the presence of HS (Labate *et al*., 2006; Labate *et al*., 2008; Labate *et al*., 2011). Our results further confirm that TPM, even at low doses, is very effective and well tolerated in partial-onset epilepsy with mild outcome. In fact, the dosage evaluated in this work ranged from 50 to 600 mg/day.

We observed, over a period of more than two years, 41 consecutive patients who were referred to our clinic with either benign or symptomatic temporal lobe epilepsy. TPM was administered at a common dosage on average of 200 mg daily. Simple and complex partial seizures dramatically improved in response to TPM and in fact 38 patients achieved seizure reduction. Of these, 28 subjects obtained seizure freedom and the remaining 10 patients achieved more than 50% reduction in seizure frequency. Interestingly, seizure freedom was experienced mainly among patients with bTLE (19 of 28 patients) who received TPM *de novo*. Moreover, for nine of 12 patients with sTLE, seizure freedom was observed. The efficacy of TPM was consistent even as add-on therapy. In this small subgroup of patients (n=12) taking different concomitant AEDs that

were quickly withdrawn throughout the follow-up, the effect of TPM cannot be attributed to pharmacokinetic or pharmacodynamic interactions.

The present study reinforces the awareness of the safety profile of TPM, similar to previous reports. Indeed, side effects were not observed in any patients except for one patient, demonstrating that TPM was very well tolerated. Nevertheless, as in other TPM trials (El Yaman *et al*., 2007), a gradual and not excessive decrease (average of 2 kilograms) in body weight occurred during TPM therapy in four patients. No clinical noteworthy findings were reported based on clinical laboratory tests, neurological examinations, or physical examinations.

TPM is effective for a broad spectrum of epileptic syndromes and our data suggest that TPM might be a very good alternative to other AEDs such as carbamazepine commonly used for the treatment of partial-onset seizures, especially for patients with bTLE. Clearly, future studies using a double-blind approach would strengthen our findings in the same population.

Interestingly, TPM that is widely used preventively against migraines also significantly improved migraine attacks in most of our epileptic patients.

TPM, which acts at different neural transmission levels, has been reported to have a selective antagonist effect on the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid AMPA/kainate glutamate receptor (Siniscalchi *et al*., 2010). Previous reports showed that the AMPA/kainate glutamate receptor is involved in temporal lobe epilepsy (Artinian *et al*., 2011) and in the genesis of migraine (Andreou and Goadsby, 2011). Therefore, a possible explanation of the positive effects of topiramate in our patients could be the modulation of AMPA/kainate glutamate receptors.

In conclusion, our results show that nearly two thirds of TLE patients treated with TPM remained seizure-free during follow-up. Once titrated to an effective dose, TPM may therefore be used as a first drug for the treatment of patients with TLE, especially with mild course and associated migraine. □

Disclosures.
The authors report no conflicts of interest.

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