

ONE-YEAR OBSERVATION OF TOPIRAMATE IN ADD-ON THERAPY IN PATIENTS WITH DRUG RESISTANT EPILEPSY

Joanna Jędrzejczak^{1,3}, Krzysztof Owczarek^{2,3}

¹ Department of Neurology and Epileptology, Medical Center for Postgraduate Education, Warsaw, Poland

² Department of Medical Psychology, Medical University of Warsaw, Warsaw, Poland

³ Teaching Center for Epileptology and Other Paroxysmal Events, Epileptology Foundation, Warsaw, Poland

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SUMMARY

Introduction. Topiramate (Topamax, TPM) is an effective AED, used to treat simple partial, complex partial and secondary generalised to tonic seizures. The drug's pharmacokinetic profile and the outcomes of clinical trials suggest that TPM may be used in both polytherapy and monotherapy.

Objective. The aim of the study was to conduct a one-year observation of the effectiveness and safety of topiramate in patients with drug resistant epilepsy in the form of partial seizures with or without secondary generalisation.

Material and methods. 86 patients (36 F, 50 M) were studied. The mean age of the patients was 30 years (13-61) and the mean duration of epilepsy was 19 years (2-55). Thirty-seven (41.2%) of the 86 patients with partial seizures had secondary generalised seizures, 8 (8.9%) had secondary generalised to tonic-clonic seizures, and 41 (45.5%) had both types. The drug was administered twice daily for a mean daily dose of 5.2 mg/kg (0.8 - 11.7). The patients were observed for 12 months.

Results. Reduction of seizures by at least 50% was observed in 47 patients (54.7%), of whom 14 patients (16.3%) attained 100% relief of seizures, while seizure reduction exceeding 50% was observed in 33 patients (38.4%). Reduction of seizures by less than 50% was observed in 39 patients (45.3%). These figures were stable throughout the entire follow-up period. Side effects

were registered and treatment was discontinued in 20% of the patients. Our clinical experience to date suggests that tolerance to TPM does not develop despite prolonged treatment with the drug. Only a small percentage of patients had to discontinue treatment due to clinical deterioration in the form of increased frequency of seizures.

INTRODUCTION

Topiramate (TPM) is a new generation antiepileptic drug whose action is multi-faceted and whose underlying mechanisms are diverse (Shank et al., 1994; Kanda et al., 1996; White et al., 1997; Kawasaki et al., 1998; Patsalos, 1999). The drug's multiple action on CNS structures not only curbs the spread of seizure activity but also raises the seizure threshold. Topimarate is effective in the treatment of simple partial, complex partial and secondary generalised to tonic-clonic seizures (Kozik, 2000; Zwoliński, 2000; Majkowski & Żyto, 2001). Reports have also been published suggesting the feasibility of using topimarate to treat primary generalised nonconvulsive seizures in children (Cross, 2002). The pharmacokinetic profile of TPM indicates that the drug can be used successfully in monotherapy (monotherapy beginning with two-year-olds has been reported). Treatment-facilitating parameters include:

- a wide spectrum of action;
- long half-life;
- possibility of administering either once daily or twice daily;
- slight and transient adverse effects (Shank et al., 1994).

Everyday clinical practice suggests that although new AEDs, including TPM, are now being more widely used, the switch to new forms of medication is often made very rapidly, without observing the patients for a long enough time. Meanwhile, prolonged and careful observation of seizure frequency (monthly averages) suggests that patients with various types of focal seizures may show certain fluctuations in the rate of improvement (Jędrzejczak & Owczarek, 2000).

The purpose of our study was to evaluate the effectiveness of TPM as add-on, one-year therapy of patients with drug resistant simple partial, complex partial and secondary generalized seizures by analyzing mean seizure frequency and standard deviations.

MATERIAL AND METHODS

The study was run on 86 patients (36 females and 50 males), mean age 30 (13-61), mean body weight 66.9 kg (20-110), mean duration of epilepsy 19.2 years (2-55). The etiology of the epileptic seizures was unknown or unclear in 53.3% of cases, and identified in 47.7% of cases. In the 43 patients with identified etiology, the following origins were found:

- perinatal lesions 23.3%;
- post-inflammatory etiology 7.8%;

- injury 7.8%;
- tumor 4.5%;
- vascular malformation 3.3%.

Partial seizures were diagnosed in 37 of these patients (41.2%), including partial complex seizures (33 patients), simple seizures only (4), and mixed simple and complex seizures (8). Eight patients (8.9%) had secondary generalised to tonic-clonic seizures. Both types of seizures, i.e., partial and secondary generalised, were identified in 41 patients (45.5%). The criterion for drug resistance was at least one tonic-clonic seizure a month or at least two partial seizures within three consecutive months. The mean number of seizures before introduction of TPM was 54 a month (1-200) for partial simple seizures, 6.9 a month (2-30) for partial complex seizures and 4 a month (1-30) for secondary generalised to tonic-clonic seizures. Before TPM was introduced, 51 patients (59.3%) had been taking 1 AED, 32 patients (37.2%) had been taking more than one (2 or 3) AEDs, and three patients (3.5%) had not been treated with any AED. The drugs most frequently taken in bitherapy with topiramate were carbamazepine (31 patients), lamotrigine (11 patients), and oxcarbazepine (6 patients). Before TPM was added on, the patients had been treated conventionally, and the therapeutic concentration of the drug in the serum had been maintained. The therapeutic concentration was more than 8 and less than 12 µg/ml for carbamazepine, more than 80 and less than 120 µg/ml for valproic acid, more than 15 and less than 30 µg/ml for phenobarbital, and more than 10 and less than 20 µg/ml for phenytoin. The new-generation drugs were administered in therapeutic doses. The doses of AEDs administered in combination with TPM remained unaltered throughout the entire observation period.

TPM was introduced after three months of observation. At first, the dose was 12.5 mg a day and then, if necessary, it was systematically increased by 12.5 mg once a fortnight.

The target dose for topiramate was 50-700 mg a day, administered twice daily. The mean dose per kg of body mass was 0.8-11.7 mg a day (mean 5.2 mg). All patients were observed for 12 months. From the very beginning, the patients were checked once a month, every month for twelve months. Seizure frequency and drug dose were registered at every visit. Any adverse events were also registered.

In order to evaluate treatment success, the patients were divided into three groups:

- group I – complete seizure remission (100%) within 12 months;
- group II – seizure reduction by at least 50%;
- group III – seizure reduction by less than 50%.

The mean frequencies of simple partial, complex partial and secondary generalized to tonic-clonic seizures by TPM dose were analyzed once a month for one year following introduction of TPM. Treatment success was evaluated by comparing the number of seizures, monthly, compared with the base-

line (i.e., three consecutive months prior to introduction of TPM). Treatment progress was evaluated by comparing the mean number of seizures between the baseline and the means for consecutive months of treatment. The statistical significance of differences was estimated by means of Student's t test.

RESULTS

In this group of 86 patients in TPM polytherapy for 12 months, seizure reduction by more than 50% was observed in 47 patients (54.7%), of which number 14 patients (16.3%) achieved complete seizure remission. Seizure reduction by less than 50% was observed in 39 patients (45.3%).

A detailed account of the one-year observation of the frequency of simple partial seizures per month by TPM dose per kg of bm. is presented in Fig. 1.

Following introduction of TPM, the frequency of simple partial seizures dropped gradually within the first four months of observation. The differences between the mean number of simple partial seizures in the baseline period and in months 4, 5 and 6 of observation, and then months 11 and 12, are statistically significant ($p < 0.05$). Between month 4 and 6 of TPM treatment, there were practically no significant differences in the mean frequency of seizures (plateau phase) despite the gradual increase of TPM dosage. Between months 6 and 7 of treatment, the mean dosage increased slightly (from 254 to 264 mg), whereas the mean number of seizures clearly increased. There is a noteworthy increment in the value of the standard deviation, suggesting increased dispersion of the results around the mean.

In those cases where complex partial seizures were present at the onset of TPM therapy, a steady, statistically significant decrement in the mean frequency of seizures compared with baseline was observed (Fig. 2). In the first month of TPM treatment, the mean number of seizures was markedly re-

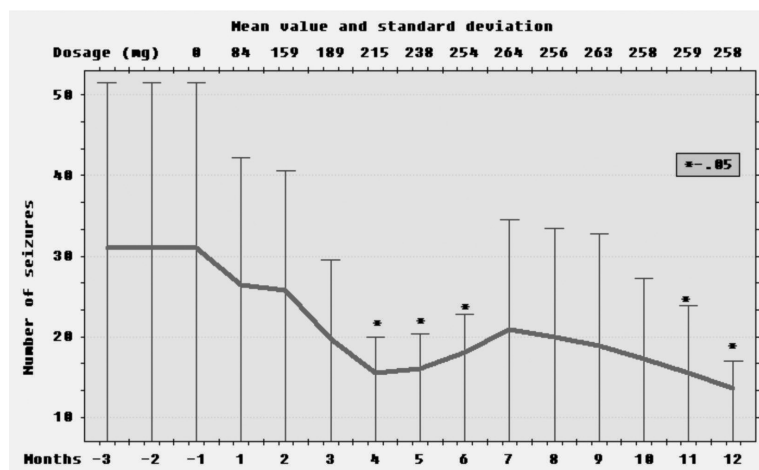


Fig. 1. Mean number of partial simple seizures in consecutive months of treatment

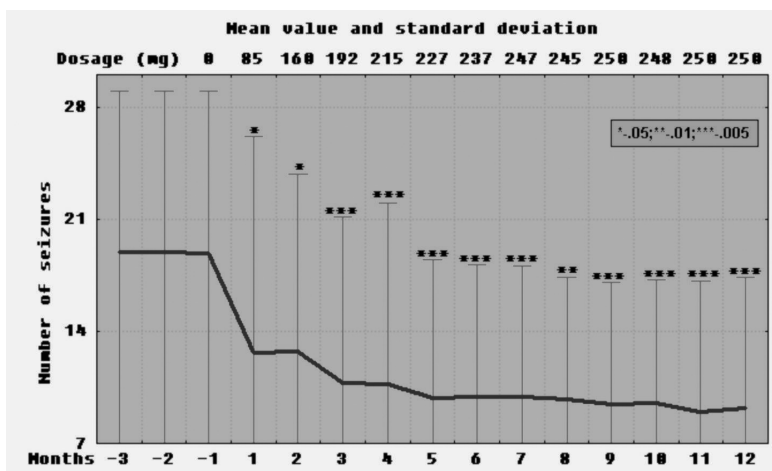


Fig. 2. Mean number of partial complex seizures in consecutive months of treatment

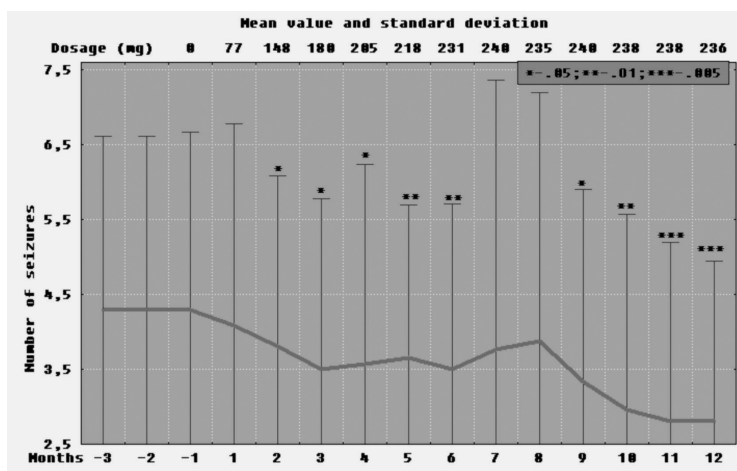


Fig. 3. Mean number of generalized seizures in consecutive months of treatment

duced. The average diurnal dose at the time was only 85 mg. In the second month of treatment, the average TPM dose increased from 85 to 160 mg.

The mean frequency of seizures compared with the end of the first month of treatment remained unchanged. Between months 2 and 3, a slight reduction of seizure frequency was observed. The average TPM dose increased from 160 to 192 mg. Between months 3 and 4 of TPM treatment, the frequency of seizures remained stable (the average TPM dose increased from 192 to 215 mg). Between months 4 and 5, there was a further minor reduction of seizure frequency (at an average dose increase from 215 to 227 mg). Between months 5 and 12 the situation stabilized: despite the further increase in mean TPM dose (from 227 to 250 mg), the mean frequency of seizures remained practically unchanged.

As with partial seizures, secondary generalized to tonic-clonic seizures showed an initial reduction in frequency (Fig. 3) up to months 7-8 of treatment, when the number of seizures increased once again. The TPM dose at this time was 231-235 mg. Between months 8 and 12 there was another clear-cut drop in the mean number of seizures.

Within the 12-month observation period, 42 patients (48.8%) had adverse events. Twenty-five patients (59.5%) lost weight, 5 (11.9%) became aggressive, 6 (14.3%) had paresthesias, 4 (9.5%) complained of insomnia and 2 (4.8%) complained of fatigue. Treatment was discontinued in 6 patients (14.3%) due to excessive weight loss (over 10%) in 4 patients and mounting aggression in 2 patients.

DISCUSSION

The average number of simple partial, complex partial and secondary generalized to tonic-clonic seizures decreased significantly compared to baseline within the 12 months following introduction of TPM. This reduction could already be observed in the first month of administration of TPM. As far as simple partial seizures are concerned, three different stages of drug effectiveness may be distinguished. Following an initial period of clear-cut improvement, the mean number of seizures clearly increases between month 6 and month 7 of treatment in spite of increased drug dosage, and therefore it is rather improbable that this deterioration can be attributed to the drug dose. The increasing standard deviation and the within-group distribution of seizures suggest that the effects of therapy began to polarize at this time. Many patients had complete remissions, whereas others demonstrated a clear-cut increase in the number of seizures. Once this pivotal (second) phase of treatment had passed, a third phase began, in which patients improved and once again seizures became less frequent. As far as partial complex seizures are concerned, a very significant reduction in the frequency of seizures was already observed in the first month of treatment, and fluctuations in seizure frequency were relatively small throughout the entire period of observation.

Analysis of the mean number of secondary generalized to tonic-clonic seizures with stabilised drug dosage revealed a similar, unstable tendency, i.e. clear-cut improvement manifested in the reduction of the average number of seizures between months 1 and 3, and from months 5 to 6 after introduction of TPM, and a slight increase in the average number of seizures between months 3 and 5 and months 6 and 8. Analysis of the dynamics of average seizure frequency suggests that, when patients are observed over a longer span of time, periods of increased effectiveness of TPM treatment of generalised seizures and periods of reduced effectiveness alternate. Another finding that calls for attention is the high value of the standard deviations in the period of reduced effectiveness, indicating that some patients had a definite increase in the number of seizures, whereas other patients showed clear im-

provement and a few even had complete remission of seizures. This clearly implies that there are critical periods in the treatment of secondary generalised to tonic-clonic seizures with topiramate. The available data do not reveal any plausible reason for the transient decrease in TPM effectiveness. The lack of any significant correlation between drug dose and frequency of seizures in these critical periods suggests that the relapse probably has nothing to do with the TPM dose. Perhaps the observed variance of outcomes could be explained if the problem were investigated at the metabolic level. Increased frequency of epileptic seizures in some patients undergoing anti-epileptic treatment with AEDs is a familiar phenomenon and has been discussed elsewhere (Bialer et al., 2002). The phenomenon has mainly been observed in patients with primary generalised seizures; however, reports based on objective, quantitative analyses are scanty. Somerville (2002) has published the results of a controlled placebo study of patients with partial seizures. In this study, patients in add-on therapy (tiagabine, topiramate and levetiracetam) demonstrated increased seizure frequency, but this increase was no greater in the treated group than in the placebo group. We may therefore assume that the transient increase in seizure frequency in our study can be attributed to spontaneous fluctuations.

One interesting aspect of the interpretation of our findings concerning the effectiveness of topiramate in polytherapy may be the incidence of drug interaction. There are only a very few published reports on the combination of topiramate with other antiepileptic drugs.

In our study, only two patients were taking phenytoin; however, these patients were also taking a third AED, in addition to topiramate, and therefore it is very difficult to interpret the possible interactions among the three drugs. The fact that relatively few patients were involved may suggest that this potential interaction had a statistically negligible effect on the observed trends.

Topiramate may increase serum concentration of phenytoin, and it may also slightly reduce the concentration of valproic acid (Gisclon et al., 1994; Rosenfeld et al., 1997). The effects of other antiepileptic drugs on TPM are either insignificant or significant.

If, in the other hand, we look for the causes of the variability we found in our study in the patients' lack of consistent adherence to the treatment regimen, then we must raise the following question: why does this factor emerge in so many patients at the same time? This explanation is all the less plausible that the patients had no reason to be disappointed with their treatment at the critical time.

One potentially important clinical aspect should be mentioned. In view of the patients' deterioration (increased seizure frequency), many clinicians conclude that the drug they are administering is not successful enough and withdraw it. In the presented study, a brief period of reduced effectiveness of the drug in some patients was followed by considerable improvement, manifested in the reduction of seizure frequency and the standard deviations for

the entire sample. Similar treatment dynamics were observed when annual progress was monitored in a group of adult patients taking vigabatrine as an add-on drug to carbamazepine (Jędrzejczak & Owczarek, 2000). A two-year study (Kozik et al., 2000) of the effectiveness of vigabatrine in polytherapy of drug resistant epilepsy in children also revealed periodic reduction of drug effectiveness, although tolerance to vigabatrine had not developed.

CONCLUSIONS

Three groups of patients treated with topiramate showed satisfactory response to the drug in the first few months of treatment, expressed in a statistically significant reduction in the average frequency of epileptic seizures. As treatment continued, however, some patients showed periodic reductions of drug effectiveness. Many clinicians withdraw drugs if seizure frequency tends to increase. It is important to remember, however, that periods of reduced effectiveness are followed by considerable improvement expressed in a substantially reduced seizure frequency. Is it justified, then, to withdraw topiramate in the initial phase of treatment with this drug (the first six months)?

It is also important to note that although analysis of drug effectiveness based on comparisons of mean values in consecutive months reflects the variance of mean values, it tends to blur individual differences in responding to the drug. If we remember to look at the standard deviations (SD), we can monitor treatment effectiveness from a more individual perspective.

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Address for correspondence:
Prof. Krzysztof Owczarek, Ph.D.
Department of Medical Psychology,
Medical University of Warsaw,
Trojdena 2,
02-109 Warszawa, Poland
cell: 0 608 491986
e-mail: krzysztof.owczarek@am.edu.pl

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