Topiramate as a long-term therapy in children with refractory epilepsy

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ABSTRACT

الأهداف: تقييم الكفاءة طويلة المفعول والسلامة ومعدل الاحتباس لعقار توبيراميت (TPM) في الصرع الطفولي العصبي.

الطريقة: صممت هذه الدراسة كمركز مفرد ودراسة وصفية استعادية. شملت الدراسة الأطفال الذين يعانون من الصرع العصبي والذين خضعوا للمتابعة الطبية في مستشفى بيهسيت يو للأطفال – تركيا، خلال الفترة بين عام 2003م وحتى عام 2007م.

النتائج: تكونت الدراسة من 43 ذكر (60.6%)، و28 أنثى (39.4%) تراوحت أعمارهم بين 2-18 عاماً. بلغ متوسط العمر8.83 عاماً (SD:3.77) وبلغ متوسط فترة الصرع 3.89 عاماً (SD:1.51) عاما. كان هنالك 41 طفلاً (57.7%) يعانون من تخلف عقلي، 27 طفلاً يعانون من شلل عام، و44 طفلاً يعانون من شلل موضعي– مرتبط. ظهرت على 51 طفلاً (71.8%) استجابة جيدة للمعالجة الأولية. بلغ معدل الاحتباس في متوسط 32 شهراً 31 من 71 من الأطفال (43.6%)، وتقريباً 18 من الأطفال (25.3%) خالين من الصرع. ظهرت فقدان الكفاءة للاستعمال طويل المدى على 17 (33.3%) من الاستجابات الأولية. تمت رؤية الأحداث المعاكسة لدى 20 طفلاً (28.1%). لم يكن هنالك فروقات ملحوظة للاستعمال على المدى الطويل بين المجموعة التي واصلت تلقي المعالجة بعقار(TPM) وتلك التي توقفت عنه.

خاتمة: كنتيجة، لقد تحدد أن العقار كان أكثر فعالية وتحملاً بشكل جيد في حالة الصرع الموضعي– المرتبط عند المتابعة على المدى الطويل.

Objective: To evaluate the long-term efficacy, safety, and retention rate of topiramate (TPM) in childhood refractory epilepsies.

Methods: This study was designed as a single-center, retrospective study. Children with refractory epilepsy who has been followed in Behcet Uz Children's Hospital, Izmir, Turkey, between 2003 and 2007 were included in the study.

Results: The study population consisted of 43 boys (60.6%) and 28 girls (39.4%) aged between 2-18 years. Mean age was 8.83 (SD: 3.77) and mean duration of epilepsy was 3.89 (SD: 1.51) years. There were 41 children (57.7%) with mental retardation. Twenty-seven children had generalized epilepsy, and 44 children had localization-related epilepsy. Fifty-one children (71.8%) showed a good response to initial treatment. The retention at a mean of 32 months was 31 out of 71 children (43.6%), and approximately 18 children (25.3%) were seizure free. A loss of efficacy in long-term use occurred in 17 (33.3%) of initial responders. Adverse events were seen in 20 children (28.1%). There were no significant differences between the groups who continued and discontinued TPM treatment in long-term use.

Conclusion: As a result, it was determined that the drug was more effective and well tolerated in localization-related epilepsies, on long-term follow up.

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Topiramate (TMP) is a broad spectrum antiepileptic drug with a multiple mechanism of activity.[1] Previous studies have shown that TPM is an effective drug on localization-related and generalize refractory epilepsies.[2-5] However, since long term treatment is the issue in refractory epilepsies, long term efficacy profiles of new antiepileptic drugs are needed to be known in clinical practices. However, there are only a small number of clinical studies on children related to efficacy

and safety of TPM in long-term use with refractory epilepsies.[6-8] In many studies, the retention rate has been shown to be the best indicator in demonstrating clinical benefits. The retention rate is considered to be a composite of drug efficacy and drug safety, and express the willingness of children to continue drug treatment.[9] This retrospective study aimed to evaluate the long term efficacy, safety, and retention rate of TPM in childhood refractory epilepsies.

Methods. This study was conducted in Behcet Uz Children's Hospital, Izmir, Turkey, as an open-label, single-center, retrospective study on children who have been followed up after a diagnosis of refractory epilepsy for the last 5 years (between 2003 and 2007). Children were selected according to the following criteria: seizures refractory to at least 2 first-line major antiepileptic drugs, and ≥2 seizures in the previous 3 months. Epilepsy, and seizures were classified using the International League Against Epilepsy (ILAE) classification.[10] Exclusion criteria were patients with progressive neurological diseases, and patients who did not reach a specific assessment point due to a recent start with another drug. The age and gender of the children, the type and etiology of their epilepsies, frequency of their seizures, adverse events, presence of mental retardation, initial dose, the dose at which seizures were controlled, and duration and efficacy of the medication were recorded. Topiramate was administered at a twice daily dose of 0.5-2 mg/kg, followed by increasing titration at increments of 1-2 mg/kg weekly until the minimum effective dose was reached. During the treatment, in all children, general clinical and neurological examination was evaluated every 3-6 months. At each assessment the total number of seizures in the time interval were analyzed using a seizure diary and unwanted effects with a questionnaire, as a standard of care at our center. Complete peripheral blood counts, urinary analysis, blood creatinine, alanine, aspartate aminotransferase levels, and renal ultrasound were also performed. Response to TPM was evaluated as complete response (100% reduction in seizures), partial response (50-98% reduction in seizures), unmodified (less than 50% reduction in seizures), and worsened (increased the seizure frequency). Retention of TPM was defined as the percentage of children still taking TPM after a mean period of 32 months of follow-up (range 20-44 months). Loss of efficacy was defined as the return to the baseline seizure frequency. Initial efficacy of TPM defined as the number of responsive children after a mean of 6 months of follow-up. The patients with initial responder to TPM treatment (Group I) were compared with the patients who discontinued TPM treatment (Group II). The Statistical Package for Social Science Version12.0 (SPSS Inc, Chicago, IL) was used. The collected data were analyzed using Epi Info version 6, and differences between groups were examined by chi-square (χ^2) test. $P<0.05$ was considered statistically significant.

Results. The study population consisted of 43 boys (60.6%), and 28 girls (39.4%) aged between 2-18 years. Mean age was 8.83 (SD: 3.77) and mean duration of epilepsy was 3.89 (SD: 1.51) years. There were 41 children (57.7%) with mental retardation. Twenty-seven children were followed up as refractory generalized epilepsy, and 44 children were refractory localization-related epilepsy (**Table 1**). When TPM initiated: 62 children used 2 drugs, 8 children used 3 drugs, and one child used 4 drugs with an average of 2.1 drugs being used. The mean TPM dose that provided seizure control was 5.26±3.01 (1-15 mg/kg). Fifty-one children (71.8%) showed a good response (complete and partial response) to initial treatment. Twenty-four (33.8%) showed complete response and 27 (38%) had partial response. The drug was found to be more effective (77.2%) on localization-related epilepsies compared to generalize epilepsies (62.9%) (p=0.007). There were no significant differences found with initial TPM effectiveness and etiology of the refractory epilepsies

Table 1 - Demographic and baseline characteristics of children receiving topiramate (n=71).

Attribute	n (%)
Age (years)	
Range	2 - 18
Mean	8.83
Gender	
Boys	43 (60.6)
Girls	28 (39.4)
Duration of epilepsy (years)	3.89
Mental retardation	41 (57.7)
Mean duration of TPM use (months)	32.4

TPM - topiramate

Table 2 - Initial response of children with epilepsy to topiramate treatment according to their etiology.

Initial responses	Symptomatic n=49	Idiopathic n=18	Cryptogenic n=4	*P*-value
	n (%)	n (%)	n (%)	
Complete response	14 (28.6)	8 (44.4)	2 (50)	0.371
Partial response	19 (38.8)	7 (38.9)	1 (25)	0.858
Unmodified	13 (26.5)	3 (16.7)	1 (25)	0.702
Increase	3 (6.1)	0	0	0.495

$p<0.05$ was considered significant

Table 3 - Evaluation of children who continued and discontinued the TPM treatment.

Characteristics	Group I	Group II	*P*-value
Age (mean)	8.6	8.8	0.819
Gender			
Girl	20	8	0.834
Boy	31	12	
Epilepsy			
Partial	34	10	0.303
Generalize	17	10	
Mental retardation	26	15	0.183

TPM - topiramate

(**Table 2**). In the evaluation after the first 6 months, adverse events were found in 17 children (23.9%), these were deterioration in cognitive functions in 3 children (4.2%), anorexia in 5 children (7%), anorexia accompanied with drowsiness in one child (1.4%), weight loss with anorexia in one child (1.4%), weight loss in 2 children (2.8%), nausea in one child (1.4%), nephrolithiasis in one child (1.4%), somnolence in one child (1.4%), rash in one child (1.4%) and nervousness in one child (1.4%). Some of the side effects resolved by slowing the rate of drug titration or reducing the TPM dosage. Due to the adverse events, 6 children (8.4%) and 3 children (4.2%) had to discontinue the drug in 3 months and 6 months. After a mean follow up of 32 months, deterioration in cognitive functions was seen in 2 children, changes in mood in one child and of loss of efficacy in 17 of 51 children, and the drug was tapered off.

The retention at a mean of 32 months was 31 of 71 children (43.6%) and approximately 18 children (25.3%) were seizure free. Loss of efficacy has occurred in 17 of 51 children in whom an effect was obtained initially (33.3%). A loss of efficacy occurred predominantly in the generalized epilepsies. A well-sustained efficacy was noted among children with refractory localization-related epilepsy (24/34). Children were divided into 2 groups according to whether they continued TPM treatment (Group I) or discontinued TPM treatment (Group II). There were no significant differences between the groups regarding age, gender, epilepsy types (partial or generalized), and the presence of mental retardation (**Table 3**).

Discussion. This retrospective study showed that TPM lost its efficacy or caused adverse events on some children in long-term follow-up, and it could be discontinued. The rate of the children on whom the medication was effective after an average of 32 months was 43.6%. A loss of efficacy occurred in 33.3% of the initial responders. Grosso et al[7] evaluated the long-term efficacy of TPM in treating children with drug-resistant epilepsy and found that the retention at a mean of 30 months was 20%, 3.5% were still seizure free (lower rates than our study). A loss of efficacy occurred in 58% of the initial responders. A higher rate than in our study, possibly, due to the higher number of antiepileptic drugs previously tried before introducing TPM treatment. We obtained complete seizure control in 33.8%, and ≥50 reduction of seizure frequency in 38% of the children with initial treatment. This higher rate obtained in our study was thought to be relevant with preference of TPM as a third drug in 61 cases (85.9%). This suggested that with early addition of TPM to the treatment, better results could be obtained. In accordance with our results from 224 patients with refractory epilepsies, 78% had a ≥50 reduction of seizures and 25% of them had complete seizure control.[11] Topiramate appeared to be more effective in cryptogenic (75%), and idiopathic (83.2%) epilepsies compared to symptomatic epilepsy (67.2%). In a previous study, TPM was also found to be effective in 76.2% of cryptogenic partial epilepsies and in 58.8% of symptomatic epilepsies.[12]

In our study, there were no significant differences found with TPM effectiveness and etiology of the refractory epilepsies. Mohamed et al[13] reported that drug discontinuation was needed in 25 (49%) of the children. Similarly in our study, TPM was discontinued in 40 children (56.3%), with 28 ineffective, 3 long-term, and 9 initial adverse events. The adverse events confirmed in 20 (28.1%) of the children were not life-threatening comparable to other studies.[13,14] The most common side effect was determined to be anorexia, and weight loss in 10 children (14%). Yeung et al[14] reported a retrospective assessment of the use of TPM in drug-resistant childhood epilepsies that consisted of 34 children, adverse effects were found in 9 (26.4%) children, appetite suppression occurred in 5 cases, behavior disturbances in 3, somnolence in 2, and poor concentration in one case. Moreland et al[15]and Uldall and Buchholt[16] reported higher rates (38% and 39%). These effects were dose dependent, and reduced by slowing the titration process. Despite deteriorations in behavioral, and cognitive functions were found to be more frequent in studies which included adult patients, it was reported that, especially in mentally retarded children this effect would be difficult to determine.[7] We did not find any ophthalmologic and hematologic adverse event. It is known that TPM may cause metabolic acidosis, and nephrolithiasis by carbonic anhydrase inhibitory effect.[17] In our study, we also found nephrolithiasis in one (1.4 %) of our children.

In conclusion, long term follow up of TPM has a few but tolerable unwanted effects. Although, it was

determined that the drug could be discontinued, we found the higher retention rate in our clinical setting.

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