Topiramate for the treatment of intractable childhood epilepsy

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ABSTRACT

Objectives: Topiramate (TPM) is a new antiepileptic drug, which has a wide spectrum of activities suggesting a potentially valuable therapeutic profile. Our objective is to report our experience in treating children with intractable epilepsy.

Methods: Prospective, open label, add on trial of TPM in treating consecutive children with intractable epilepsy (defined as recurrent seizures after at least 3 antiepileptic medication trials) seen between May 1, 1999 and April 28, 2002 at King Faisal Specialist Hospital and Research Centre and King Abdulaziz University Hospital in Jeddah, Kingdom of Saudi Arabia. Follow up by 2 pediatric neurologists was performed. Therapeutic response was recorded as complete (no seizures), good (>50% seizure reduction), fair (<50% seizure reduction), or none.

Results: Sixty-two children (36 males and 26 females) aged between 2 months and 16 years (mean 6 years) were treated with TPM and followed for up to 3 years (mean 15 months). Most children (55%) had daily seizures and were tried on multiple antiepileptic drugs (mean 4.6). Nineteen (31%) children had Lennox-Gastaut syndrome. After the introduction of TPM, 21 (34%) became completely seizure free and 24 (39%) had >50% seizure reduction. Children with daily seizures were reduced from 55% before TPM to 13% on TPM (p=0.0007). Side effects were reported in 21 (34%) children in the form of decreased appetite, weight loss, and sedation. The majority was transient; however, TPM had to be withdrawn in 7 (11%) children because of progressive weight loss or seizure worsening. Follow up renal ultrasound was performed on 34 (55%) children and was always normal.

Conclusions: Topiramate is a very effective antiepileptic drug with a broad spectrum of antiepileptic activities. Most side effects were transient, however, careful monitoring of body weight is recommended.

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Intractability in childhood epilepsy has been associated with cognitive and behavioral problems and impaired psychosocial development.[1,2] Therefore, these children have a high potential for a long-term disability and difficulties in adjusting to school.[3] Recurrent seizures also increase the risk of injury and even death.[4-6] Improved seizure control should therefore decrease these risks and improve the quality of life in these children. Topiramate (TPM) is a new antiepileptic drug (AED), which appears to have multiple modes of action including sodium channel blockade, gamma-aminobutyric acid enhancement, glutamate antagonism, and weak carbonic anhydrase inhibition.[7-9] This wide spectrum of antiepileptic actions suggests a valuable and broad therapeutic profile. There are an increasing number of clinical trials describing the response of children with various types of epilepsy to TPM.[10-21] Clinical trials have shown that TPM is effective when used adjunctively in children with refractory partial and secondary generalized seizures.[13,18] It was also found to be useful as adjunctive therapy in the management of primary generalized tonic clonic seizures, Lennox-

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Gastaut syndrome, severe myoclonic epilepsy of infancy, and West syndrome.[13-15,19-21] Topiramate was introduced in the Kingdom of Saudi Arabia (KSA) in 1999. To date, no regional data evaluating the experience in Saudi children has been published. In this paper, we report our experience with TPM for the treatment of children with intractable epilepsy.

Methods. A series of consecutive children with intractable epilepsy was identified prospectively starting on May 1, 1999 to April 28, 2002. Patients were identified through referrals and consultations to the pediatric neurology service at King Faisal Specialist Hospital and Research Centre (KFSH&RC) and King Abdul-Aziz University Hospital, both in Jeddah, KSA. King Abdul-Aziz University Hospital is the main teaching center of the western region in collaboration with KFSH&RC. Both are multispecialty adult and pediatric hospitals providing tertiary medical care for most of the regional population of western Saudi Arabia. Patient and disease related data was collected during the initial visit. Intractable epilepsy was defined as recurrent seizures that failed to respond to at least 3 antiepileptic drug (AED) trials singly or in combination despite using maximum doses or doses resulting in therapeutic drug levels. After obtaining verbal consent, TPM was added to the other AED therapy at a starting dose of 12.5-25 mg/day. The dose was doubled every week until the minimum effective dose was reached (achieving a seizure free outcome) or up to a maximum dose of 10 mg/kg/day. Follow up by 2 pediatric neurologists was performed to document therapeutic response and occurrence of side effects. Therapeutic response was recorded as complete (no seizures), good (>50% seizure reduction), fair (<50% seizure reduction), or none (no response). The data was tabulated using Epi Info, version 6,[22] and the results were examined by Chi-square statistics to identify the magnitude of significant associations when present. A *p* value less than 0.05 was considered statistically significant.

Results. Sixty-two children with intractable epilepsy were included. There were 36 (60%) males and 26 (40%) females. Forty-two (68%) children had mental retardation, which was severe in 14 (33%). The underlying diagnoses and seizure classification are summarized in **Tables 1 & 2**. Brain computerized tomography scan results were available on 41 (66%) children, and were considered normal in 13 (32%). Brain magnetic resonance imaging was documented in 46 (74%) children and was normal in 15 (33%). Overall, cryptogenic epilepsy (abnormal development and central nervous system exam with no recognized disease) was the most common diagnosis (44%) as shown in **Table 1**. Nineteen (31%) children had Lennox-Gastaut syndrome (**Table 2**). The age of seizure onset ranged between one-month and 12 years (mean 23 months). The age at the time of initiating TPM therapy ranged between 2 months

Table 1 - Causes of the intractable epilepsy in the study cohort (N=62).

Diagnosis	n	(%)
Cryptogenic epilepsy	27	(44)
Syndromic/CNS malformation	12	(19)
Cerebral palsy	6	(10)
Idiopathic epilepsy	4	(6.5)
Degenerative/metabolic disorder	4	(6.5)
Post-meningitis or post-encephalitis	3	(5)
CNS tumor	2	(3)
Post-traumatic epilepsy	2	(3)
Mesial temporal sclerosis	2	(3)

CNS - central nervous system

Table 2 - Epilepsy syndromes and seizure types based on the clinical and EEG data (N=62).

Epilepsy classification	n	(%)
Lennox Gastaut syndrome	19	(31)
Mixed seizures (unclassified)	11	(18)
Frontal lobe epilepsy	6	(10)
Infantile spasms	6	(10)
Temporal lobe epilepsy	5	(8)
Primary generalized tonic clonic seizures	5	(8)
Myoclonic epilepsy	4	(6)
Early myoclonic encephalopathy	3	(5)
Severe myoclonic epilepsy of infancy	2	(3)
Absence epilepsy	1	(2)

EEG - electroencephalogram

Table 3 - Seizure count before and after the initiation of topiramate.

Seizure count	Before topiramate		On topiramate	
	n	(%)	n	(%)
Daily	34	(55)	8	(13)
Weekly	22	(35)	15	(24)
Monthly	6	(10)	18	(29)
None	-	-	21	(34)

Table 4 - EEG findings before and after the initiation of topiramate.

EEG findings	Before topiramate (n = 50)		On topiramate (n = 42)	
	n	(%)	n	(%)
Normal	-	-	17	(40)
Nonspecific slowing	7	(14)	16	(38)
Focal or multifocal spikes	19	(38)	5	(12)
Generalized epileptiform discharges	8	(16)	4	(10)
Slow spike wave discharges	10	(20)	-	-
Hypsarrythmia	6	(12)	-	-

EEG - electroencephalogram

and 6 years (mean 6 years). Most children (55%) had daily seizures and were receiving multiple AEDs (range 2-4, mean 3.2). They previously failed 4.6 AED trials on average (range 3-8).

Topiramate was added to the other AEDs at a starting dose of 12.5-25 mg/day (mean 18). The final TPM dose ranged between 50-400 mg/day (mean 135) divided twice per day, corresponding to 4.5-10 mg/kg/day (mean 7.2). The children were followed for 6 months to 3 years (mean 15 months). After the introduction of TPM, 21 (34%) became completely seizure free, 24 (39%) had >50% seizure reduction, 10 (16%) had <50% seizure reduction, and 7 (11%) had no improvement. **Table 3** shows a summary of the seizure count before and after TPM. The number of patients with daily seizure was reduced from 55% before TPM to 13% on TPM (p=0.0007). Children with Lennox Gastaut Syndrome had a relatively less favorable response as more children continued to have daily seizures when compared to those with other seizure types, and 27% became completely seizure free (p=not significant). All children continued to receive other AEDs (1-2 in addition to TPM), but the total number of AEDs was reduced from a mean of 3.2 before TPM to a mean of 1.9 while receiving TPM. Electroencephalograms (EEG) were documented before starting TPM in 50 (81%) children and repeated while the child was on it in 42 (68%). **Table 4** summarizes the EEG findings in the 2 groups and shows the significant improvements on EEG abnormalities following the introduction of TPM.

Side effects were noted in 21 (34%) children in the form of decreased appetite and nausea (18%), progressive weight loss (6%), sedation (5%), and seizure worsening (5%). Most of the side effects were transient, particularly the decreased appetite, which resolved spontaneously or with dose reduction. However, TPM had to be withdrawn in 7 (11%) children because of excessive weight loss (6%) or seizure worsening (5%). Follow up renal ultrasound was performed on 34 (55%) children and was always normal.

Discussion. The study results confirm that TPM is an effective and well-tolerated AED. Most of our patients had significant seizure reduction and one third became completely seizure free. This is very impressive given that all the children had a long history of difficult seizure disorder and one third had Lennox-Gastaut syndrome. As well, the number of AEDs also decreased following the introduction of TPM. Whenever carried out, most EEGs also showed marked improvement in terms of epileptiform discharges. Ritter et al,[18] reported their experience in children with intractable partial epilepsy.[18] Seizure frequency was reduced >50% in 57% of children and 14% were completely seizure free.[18] A recent double blind, randomized trial of TPM in 98 children with Lennox-Gastaut syndrome revealed that 30% had more that 50% seizure reduction compared to 8% in the placebo control group.[19] In an open label trial in Lennox-Gastaut syndrome, 15% had no drop attacks for at least 6 months and 55% had more than 50% seizure reduction.[20] The efficacy of TPM as adjunctive therapy for the treatment of primary generalized tonic clonic seizures was also examined in a randomized, double blind, placebo controlled study.[21] The proportion of patients with 50% or higher reduction of seizures was 46% in the TPM treated group compared to 17% for the placebo group.[21] Our seizure reduction rates were comparable to that reported in other studies, however, we had a higher seizure free outcome (34%). This could be related to the heterogeneity of our study sample, which included a variety of seizure types and epilepsy syndromes. We had a relatively longer follow up period (mean 15 months) to confirm the seizure free outcome.

Our maximum dose did not exceed 10 mg/kg/day, which was based on the other reported experiences. Preliminary data on the pharmacokinetics of TPM in young children appears to be linear with higher plasma clearance than that reported for older children, and therefore, substantially higher than that reported for adults.[16] This means that young children may require significantly larger doses per kilogram than older children and adults. These authors recommended titration to effect and not absolute TPM dose to guide therapy in this age group.[16] It is possible that higher doses (>10 mg/kg/day) may prove to be more effective in the future.

In our study, most TPM side effects were minor and the drug was well tolerated. We never encountered renal stones, however, routine renal ultrasound was performed in only 55%. The side effects were noted in 34% in the form of decreased appetite, nausea, progressive weight loss, sedation, and seizure worsening. Most of these side effects were transient, particularly the decreased appetite, which resolved spontaneously or with dose reduction. However, TPM had to be withdrawn in 11% because of progressive weight loss or seizure worsening. In one long-term response trial of TPM in West syndrome, the drug was well tolerated and no patients were discontinued because of adverse events.[15] This is also the experience of other investigators who used TPM in young children.[17] In another study, 6% of children discontinued TPM because of adverse effects and 13% discontinued because of inadequate seizure control.[18] This is similar to the findings of other investigators who found 71% of the children were continuing therapy at the last follow up visit.[20] When a lower target dose was used (6 mg/kg/day), no patient discontinued TPM due to adverse events.[19] Despite using this lower target dose, 20% of their patients also had weight loss.[19] In comparison with the other studies, we had relatively lower cognitive side effects and drug withdrawal rates. This is likely to be the result of the slow rate of drug introduction and the tendency to use the minimum effective dose. Cognitive and behavioral side effects are more common with rapid dose titration.[14] The other possible explanation is the rate of mental retardation in the study sample. Most of

our patients (68%) were mentally handicapped which may interfere with parental recognition and reporting of cognitive side effects. Recently, Takeoka et al[23] reported mild metabolic acidosis (decreased serum bicarbonate) in children treated with TPM, presumably related to carbonic anhydrase inhibition. We did not routinely screen for this abnormality in our patients. Caution is needed when TPM is used in children with conditions that may predispose to acidosis or poor weight gain.

Although long term safety and possible adverse effects of TPM have not been fully established in young children, TPM represents an option for children with high seizure frequency unresponsive to standard AEDs. We found it very effective with a broad spectrum of antiepileptic activities. Most side effects were transient, however, careful monitoring of the body weight is recommended.

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