Topiramate for the treatment of infants with early myoclonic encephalopathy

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ABSTRACT

Objectives: Early myoclonic encephalopathy (EME) is a rare epileptic syndrome characterized by neonatal onset of severe recurrent seizures of multiple types often resistant to antiepileptic drugs (AEDs). Topiramate (TPM) is a new AED, which has a wide spectrum of antiepileptic activities suggesting a potentially valuable therapeutic profile. There is limited clinical data available on TPM use in infants and our aim is to report our experience with TPM for the treatment of infants with intractable seizures secondary to EME.

Methods: Prospective, open label, add on trial of TPM in treating a series of infants with EME at King Faisal Specialist Hospital and Research Centre and King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia between June 1999 and March 2002. Topiramate was started at 12.5 mg/day and was increased by doubling the dose every week until the minimum effective dose was reached (seizure free outcome) or up to a maximum of 10 mg/kg/day.

Results: Four consecutive infants (2 males and 2 females) were included. In addition to daily seizures, they all had global hypotonia, developmental delay, and progressive microcephaly. The syndrome was cryptogenic in 3, and one had nonketotic hyperglycinemia. Initial electroencephalograms showed generalized epileptic burst suppression pattern. Infants were tried on multiple AEDs (6-11, mean 7.5) with no success. Topiramate was added at age 5-12 months (mean 9) reaching a maximum dose of 5.5-10 mg/kg/day (mean 7.6). The infants were then followed for up to 19 months (mean 13.5). After introducing TPM, one infant became completely seizure free and 3 had significant (>50%) seizure reduction. Electroencephalograms in 3 infants showed marked improvement. One infant had weight loss that resulted in discontinuing the drug after 6 months. Follow-up renal ultrasound findings were normal in all infants.

Conclusions: Topiramate is effective and safe in treating infants with intractable epilepsy secondary to EME.

Neurosciences 2003; Vol. 8 (2): 110-112

Early myoclonic encephalopathy (EME) is a rare epileptic syndrome that consists of 2 clinically similar syndromes closely related to infantile spasms.[1] These include early infantile epileptic encephalopathy described by Ohtahara et al in 1987,[2] and neonatal myoclonic encephalopathy described by Aicardi in 1990.[3] Some authors suggested that the separation between these syndromes might be artificial.[4] In this paper, we will use the term early myoclonic encephalopathy to be inclusive of both clinical entities.[5] Early myoclonic encephalopathy is characterized by neonatal presentation of severe recurrent seizures of multiple types (myoclonic, clonic, and tonic). The seizures are frequently resistant to antiepileptic drugs (AED). The electroencephalogram (EEG) shows striking epileptic burst suppression pattern that may later evolve to atypical or modified hypsarrhythmia. Early myoclonic encephalopathy can be lesional (central nervous system (CNS) malformations, migration disorders), metabolic (mitochondrial, amino acid, and organic acid disorders, especially nonketotic hyperglycinemia), or cryptogenic. Regardless of the etiology, infants with EME carry poor prognosis for complete seizure control and neuro-developmental

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Received 8th July 2002. Accepted for publication in final form 2nd October 2002.

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outcome.[1-3,5] Topiramate (TPM) is a new AED, which appears to have multiple modes of action including sodium channel blockade, gamma-aminobutyric acid enhancement, glutamate antagonism, and weak carbonic anhydrase inhibition.[6-8] This wide spectrum of antiepileptic actions suggests a valuable and broad therapeutic profile. There is limited clinical data available on TPM use in infants and young children.[9-17] However, the current clinical experience is encouraging. Clinical trials have shown that TPM is effective when used adjunctively in children with refractory partial and secondary generalized seizures.[12] It was also found to be useful as adjunctive therapy in the management of Lennox-Gastaut syndrome, severe myoclonic epilepsy of infancy, and West syndrome.[12-14] In this paper, we report our experience with TPM for the treatment of infants with intractable seizures secondary to EME.

Methods. A series of consecutive infants diagnosed with EME was identified prospectively. 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, Kingdom of Saudi Arabia, between June 1999 and March 2002. 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 KSA. Patient and disease related data was collected during the initial visit. The diagnosis of EME was based on the clinical features and EEG findings. The seizures were of neonatal onset, mixed, and intractable (defined as recurrent seizures that failed to respond to at least 3 antiepileptic medication trials singly or in combination despite using maximum doses or doses resulting in therapeutic drug levels). After consenting to drug use, infants were started on TPM in an open label, add on trial. Topiramate was added to the other antiepileptic drug therapy at a starting dose of 12.5 mg/day and was gradually increased by doubling the dose 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 one pediatric neurologist 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).

Results. Four consecutive infants (2 males and 2 females) were included. All infants had many daily seizures that started early in the neonatal period (mean age of 3 days). The seizures were of multiple types (myoclonic, clonic, and tonic), however, myoclonic seizures were the most common. There were no prenatal, natal, or postnatal complications that would explain their state. In addition these infants had global hypotonia, developmental delay, and progressive microcephaly. Brain computed tomography (CT) and magnetic resonance imaging (MRI) were performed in all cases and revealed mild nonspecific atrophy in 2. No malformations or developmental abnormalities were detected. Detailed metabolic workup was unrevealing except in one girl who had nonketotic hyperglycinemia. The syndrome was therefore cryptogenic in the other 3 infants. Initial EEGs showed generalized epileptic burst suppression pattern (**Figure 1**). The infants were tried on multiple AEDs (6-11, mean 7.5) with no success, including the newer AEDs, B6, steroids, and intravenous immunoglobulins. Before introducing TPM, the infants were receiving 2-3 AEDs. Topiramate was added to the other AEDs at age 5-12 months (mean 9). The final Topiramate dose ranged between 50-100 mg/day (mean 65) divided twice per day, corresponding to 5.5-10 mg/kg/day (mean 7.6). The infants were then followed for up to 19 months (mean 13.5). After the introduction of TPM, one infant became completely seizure free and 3 had significant (>50%) seizure reduction. All infants continued to receive other AEDs (1-2 in addition to TPM). The EEGs in 3 infants revealed marked improvement in terms of epileptiform discharges, but continued to show background abnormalities. The EEG features evolved to that of Lennox-Gastaut syndrome in one boy who was followed to the age of 27 months. No side effects or drug interactions were noted in 3 infants. One infant had initial weight loss and subsequent poor weight gain that resulted in discontinuing the drug after 6 months. Follow-up renal ultrasound was normal in all infants.

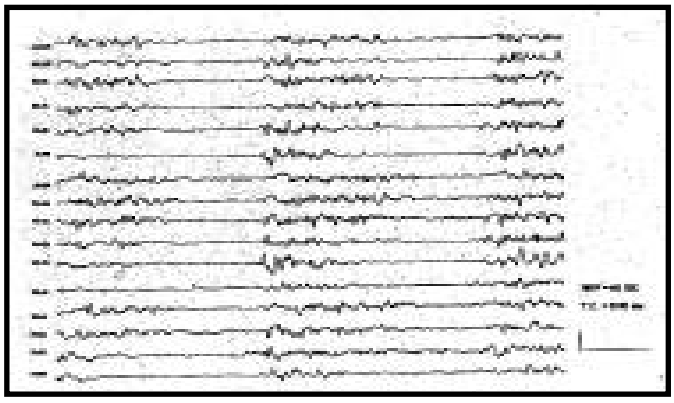

Figure 1 - Electroencephalogram (coronal montage) of a 7-month-old infant diagnosed with early myoclonic encephalopathy before introducing topiramate. The features are consistent with generalized epileptic burst suppression pattern.

Discussion. The study results suggest that TPM is an effective and well-tolerated AED when used in infants with EME. Three of our infants had significant seizure reduction and one became completely seizure free. This is very impressive, as all of them had very

difficult seizures, which were resistant to multiple AEDs. Most EEGs also showed marked improvement in terms of epileptiform discharges. Other investigators have successfully used TPM in infants primarily with myoclonic epilepsy;[13,14,16] however, there are no reports of using it in EME. Our maximum dose did not exceed 10 mg/kg/day which was based on other reported experience and the drug company's recommendations. Preliminary data on the pharmacokinetics of TPM in infants appears to be linear with higher plasma clearance than that reported for older children, and therefore substantially higher than that reported for adults.[15] This means that infants may require significantly larger doses per kilogram than older children and adults. These authors recommended titration to effect and not absolute TPM dose should guide therapy in this age group.[15] It is possible that higher doses (>10 mg/kg/day) may prove to be more effective in the future.

We did not encounter any significant side effects in 3 infants, however, TPM had to be discontinued in one infant because of weight loss. In one long term response trial of TPM in infants with West syndrome, the drug was well tolerated in that no patients discontinued because of adverse events.[14] This is also the experience of other investigators who used TPM in young infants.[16] Mild to moderate behavioral and cognitive side effects may be difficult to recognize in our young developmentally delayed patients. We used a slow rate of drug introduction and tended to use the minimum effective dose. Rapid dose titration has been implicated in these side effects.[13] Recently, Takeoka et al[17] 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 infants with conditions that may predispose to acidosis or poor weight gain.

Although long term safety and possible adverse effects have not been fully established in infants, TPM may represent an option for infants with high seizure frequency unresponsive to standard AED. We found it effective and safe in treating infants with intractable epilepsy secondary to early myoclonic encephalopathy. Careful monitoring of the body weight is needed in these patients.

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