EFFICACY AND SAFETY OF TOPIRAMATE IN THE TREATMENT OF REFRACTORY EPILEPSY IN INFANTS AND YOUNG CHILDREN: A MULTI-CENTER STUDY

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Abstract
Topiramate is a novel antiepileptic drug (AED) that has demonstrated that efficiency in this management of a variety of refractory epilepsy in children. The hypothesis of this research was to determine the safety and efficacy of topiramate on children of 60 months and below in age who were in infancy and refused epilepsy composed of Lennox-Gastaut syndrome (LGS), infantile spasms (IS), and more other epileptic disorders. This was a multi-center study in which 65 children were involved. The outcomes revealed that topiramate was tolerable and efficacious in decreasing the amount of seizures, and an enormous percentage of children got full remission or over 50 percent decrease in seizure rate. Somnolence, reduced appetite, and behavior change were typical side effects, but the level was mild and did not last long. Children with cryptogenic and LGS related epilepsy showed better response to treatment whereas symptomatic epilepsy exhibited low response. Although the results are promising, there are safety and toxicity issues that must be resolved because metabolic changes and cognitive effects were not the subject of the study. There must be additional research to access the effectiveness of topiramate in long-term based mostly in relation to the cognitive developments and metabolic actions within young children.
Keywords: Topiramate, refractory epilepsy, Lennox-Gastaut syndrome, infantile spasms, pediatric epilepsy

Introduction

Topiramate is a new age antiepileptic drug (AED), an agent that exerts its antiepileptic effects via blocking the sodium conductance pathways, and stabilizing the GABA propagated chloride influxes, and attenuating the kainate/ ampa glutamate receptors [1-3]. Topiramate efficacy and safety has been well-founded among adults and that it has been found helpful as adjunctive treatment of various seizures including localization-related seizure and Primary Generalized seizure [46].

Recent studies have reported the success of the drug in treating partial epilepsy and generalized epilepsy among the school-going children and adults [7-10]. Furthermore, topiramate is also useful in management of LennoxGastaut syndrome, (LGS) infantile spasms (IS) [11-16].

Nonetheless, not much has been said about its efficacy in babies and young children and especially the preschoolers. Hence this prospective and multi-center study was conducted so as to establish the safety and efficacy of the topiramate in the management of different types of epilepsy in children ranging between the age range of 6 to 60 months.

Methods

Such a work was carried out to study in advance the outcomes of topiramate in infants and young children with refractory epilepsy. Sixty-five kids (35 boys and 30 girls) with average

age of 6 to 60 months and unresponsive epilepsy (a repeated epilepsy, uncontrolled after various attempts of at least two AEDs in combination, having commenced with an optimal dosage or a reported therapeutic dose) were found between January 2002 and December 2002. The children were recruited in the three tertiary hospitals found in Jordan which included King Abdullah University Hospital, Princess Rahmah Teaching Hospital situated in the northern section, and King Hussain Medical Center in the Amman region. The study had been passed in the ethical committee of all the three hospitals.

Patients were included according to the following criteria: (i) 6 months old to 5 years old; (ii) refractory epilepsy (Patients with epilepsy are considered in refractory when they have an epileptic syndromes or a present comorbidity); (iii) Taking at least 2 AEDs; (iv) In progressive neurological illness. Electroencephalogram (EEG) and All patients had computerized tomography (CT) or magnetic resonance imaging (MRI) done.

Seizure diaries were used to ask parents or caregivers to report the type, duration and frequency of the seizures. In children who experienced repetitive spasms and absences that could not be measured, the parents had to record the estimated percentage change in the occurrence of the seizures each week with the following possible reports: no seizures, >50% decrease, stable, <50% decrease and worsening. The repetition of EEG was not conducted because of financial restrictions.

Seizures were characterized as (i) Infantile spasms (IS) according to the standard characteristic clinical and EEG findings, (ii) Lennox-Gastaut syndrome (LGS) according to the clinical and EEG features (mixed failure, developmental lag inclusive of intellectual disability and typical slow spike-wave discharge) and (iii) other epileptic forms in the absence of validating IS or LGS. The etiological classification of seizures addressed them as either cryptogenic or symptomatic with five children out of nine with IS having clinical diagnosis of tuberous sclerosis.

Following informed consent, they were initiated on topiramate therapy at the dose of 1mg/kg twice a day and then gradually escalated by 1 3mg/kg/day, at 2 weeks intervals until minimum dose (seizure-free outcome) corresponding to a maximum of 10mg/kg across all the ages, unless the child does not tolerate this drug.

A total of 65 children who participated in the research were observed during an average of 6 months (3 to 10 months). Side effects were observed in all participants, the levels of concomitant AEDs, the profile of liver functions, EEGs, ultra sound scan of renal, and eye examination were observed. This was not observed due to lack of the facilities to take the level of topiramate in the blood. The rating of therapeutic responses was graded as satisfactory where there was complete remission (seizure-free), and at least half reduction of the frequency of seizures. Getting 50 percent or less reduction in seizures, modification in the seizures or an increase in the seizures rendered responses unsatisfactory. Patients were obliged to come to the hospital once in a month to undergo follow-ups in order to avoid side effects or earlier in case of any issue. Data gathered were evaluated with Epi Info version 6 and the statistical difference of the groups determined by fisher exact test.

Results

The research encompassed 65 children with refractory epilepsy aged between 6 and 60 months with a mean age of 33 months (Table 1). The sample (35 boys: 54% and 30 girls: 46%) was of 65 participants. In the case of epilepsy cases, 23 percent of the children experienced symptomatic epilepsy, whereas percent of the children had cryptogenic epilepsy. Infants with epilepsy known as infantile spasms (IS) were 18 per cent, Lennox-Gastaut syndrome (LGS) was 43 per cent and 39 per cent with other discomforts of epilepsy. Also, 38 children (58%) were on two background AEDs whereas 27 children (42%) were undergoing over two AEDs.

Regarding the topiramate treatment efficacy, its response was different when it came to the various types and etiology of epilepsy (Table 2). The complete remission was enjoyed by 12 children (18%) with maximal rates in LGS group (6 children) and IS group (3 children). Improvement in the frequency of seizures by more than 50% was reported in 25 children (38%) and with highest percentage (10 children) constituted the LGS group. A total of 37 children(57 percent) showed satisfactory response and it comprised complete remission and improvement in excess of 50 percent. Of the rest children 9 (14%) achieved improvement of 0-50 percent and 13 children (20 percent) had no response and 7 children (11%) had increased seizures.
Etiology-based analysis on the more detailed analysis showed that most of the parents gave satisfactory responses where the participant had cryptogenic epilepsy (27 of 54 percent), whereas children with symptomatic epilepsy gave fewer satisfactory responses (10 of 67 percent). Poor response to treatment was more seen in symptomatic epilepsy (7 children, 47%) than in crypotgenic epilepsy (13 children, 26%).
Topiramate was, therefore, effective in the treatment of children with refractory epilepsy, especially the ones with cryptogenic and LGS-related epilepsy, but the response was somehow variable regardless of the type of epilepsy as well as the etiology.

Table 1: Demographic and Epilepsy Classification of Study Participants

Attribute	**%**
Age (months)	
Range	6–60
Mean	33
Gender	
Boys	35 (54%)
Girls	30 (46%)
Epilepsy Classifications	
Symptomatic	15 (23%)
Cryptogenic	50 (77%)
Infantile Spasm	12 (18%)
Lennox–Gastaut	28 (43%)
Other Epilepsies	25 (39%)
Background AEDs Numbers	
Two AEDs	38
More than Two AEDs	27

Table 2: Efficacy and Response of Topiramate by Epilepsy Type and Etiology

Response	**LGS (n = 28)**	**IS (n = 12)**	**Others (n = 25)**	**Total (n = 65)**	**Cryptogenic (n = 50)**	**Symptomatic (n = 15)**
Complete Remission	6	3	3	12	9	3
>50% Improvement	10	3	12	25	18	7
Total Satisfactory	16	6	15	37	27	10
≤50% Improvement	4	3	2	9	6	3
No Response	8	3	2	13	9	4
Worsened	4	2	1	7	4	3

Total Unsatisfactory	12	5	3	20	13	7

Discussion

In this study, it has proved that topiramate is a well tolerated and effective agent in the treatment of infants and young children with refractive epilepsy. The clinical outcome to topiramate was interesting in all the types of epilepsy without any measurements being notable among the clinical forms or cryptogenic and symptomatic epilepsy.

Hassan et al. also reported the same with them indicating that 34 per cent of children with intractable seizures attained seizure-freedom and 39 per cent recorded over 50 per cent decline in frequency of seizure [17]. Similar results were observed by Ritter et al. in children with partial epilepsy, where 57 percent of children reported the decrease in the symptom frequency of more than 50 percent, and 14 percent became seizure-free [18]. In the study of Coppola, et al., 2013 a group of children with refractory partial epilepsy was investigated with 20 percent obtaining a seizure-freedom and more than 50 percent reduction in frequency of seizures in 45 percent [8]. Biton et al. have also encountered a positive reaction in children with primary generalized epilepsy where 46 percent of them had over 50 percent reduction in seizure frequency as opposed to 17 percent in placebo group [4].

Lennox which is composed of Lennox and Gastaut syndrome (LGS) is incredibly hard to cure, although the reaction to topiramate in this population was better, with 60 percent of members getting a acceptable follow up. In a randomized and double-blind study, a study group Sachdeo et al. treated LGS patients with a 30 percent of the patient group having greater than 50 percent reduction in the incidence of the rate of seizures compared to 8 percent in the placebo [14]. Similarly in another study involving open-label trial on patients of LGS, it was reported that 15 percent of the patients failed to develop drop attacks and 55 percent showed diminution over 50 percent of the attacks rate because of treatment [19]. Coppola et al. and Alva Moncayo et al. used other experiments regarding LGS and have discovered that there is a prospective outcome with topiramate [15,16].

Treatment of infantile spasms (IS) is still debatable. Adrenocorticotropic hormone (ACTH), steroids, and vigabatrin are considered to be first-line treatments of IS. In this research, the infants who are IS had not responded to these therapies in the first place before being administered to the topiramate where they responded satisfactorily in 4 out of 9 instances. According to Glauser et al., topiramate would be an effective option in the management of the IS, as they asserted that 45 percent of the affected infants converted to SP free states [11]. Thiji et al. and Watemberg also suggested the same studies and indicated that the topiramate responded well in children with IS who did not respond to the standard regimens [12,13]. Observations The more recent studies that have studied the effect of topiramate in children with intractable epilepsy, including IS and LGS have found out that topiramate is effective and well tolerated among the different syndromes although data related to its use in effect in infants with IS was not studied separately [7,8,17,20]. Topiramate was found to work in 11/ 13, and was administered to children with partial and generalized refractory epilepsy. Another successful response has also been reported on past research on similar populations [710,17,20].

According to the past experiences, we used the topiramate at the highest dose of 10mg/kg/day, which we considered as the maximum dose, in our research, and reports by other researchers [717]. In infants and young children, pharmacokinetic data on topiramate available at this early stage indicate that topiramate clearance is linear, and that plasma clearance is greater than in older children or in adults [21]. It is also stated that the younger children should also be given depending on a response instead of the definite topiramate dose. This translates to the fact that in future, possibly doses larger than 10mg/kg/day might prove to be more effective [21].

As it has been noted in Table 3, topiramate was a well-tolerated drug and the side effects localized in relation to this drug were rather mild. The side effects have been found on 53

percentages of the patients with the major ones including somnolence, diminished appetite, and altered behavior. The renal stones were not examined but precautionary renal ultrasound was being carried out at every six-month interval. Majority of the side effects were temporary and were mostly somnolence and appetite suppressions which were managed either by dose modifications or spontaneously. Nevertheless, 13 percent of cases were found to have to discontinue topiramate because it aggravated the condition of seizures and resulted in steady weight loss.

Our study ratio of side-effects is more or less like that of Ritter et al, where 6 percent of the children discontinued topiramate because of side-effects and 13 percent because of poor seizure control. In a study by Glauser et al., the last follow-up visit has shown that 71 percent of children remained under topiramate treatment [18,19]. Sachdeo et al. noted that at lower target dose (6mg/kg/day), no patient dropped out due to the side effects but 20 percent of the patients lost their weights despite the dose used was low [14]. We found a smaller number of cognitive side effects (e.g. psychomotor delay) than did other studies in the same cohort. This can be attributed to rate of titration of the drug (cognitive side effects are encountered more commonly with rapid dose escalations) and use of the least effective dose [22].

Takeoka et al. have reported mild metabolic acidosis (low serum bicarbonate) in children under topiramate therapy presumable due to carbonic anhydrase inhibition, and it was suggested that care maybe exercised in application of the drug in children prone to acidosis or failure in gaining weight [23]. Acid-base balance was no routine testing that we performed in our patients. The glaucoma has also been related to topiramate therapy [24], and we examined all patients regularly through ophthalmic examination after every six months. Two of our cohort children had complaints of the eyes and have been taken to an ophthalmologist, and they have not been diagnosed with glaucoma. LGS in one patient led to development of hypothyroidism nine months following use of topiramate, but it was not clear whether topiramate was associated with hypothyroidism, because the patient was also taking other AEDs and the baseline results on thyroid functions were not known.

The study proves that topiramate is still an effective medication against children with a tremendous amount of seizes who cannot be treated with no conventional AEDs; nevertheless, the long-term safety and side effect of topiramate in the infants and very young children have not been established yet.

Conclusion

In conclusion, it can be stated that the article in question demonstrates that it is a well-tolerated and functional drug topiramate that is definitely treatment of choice in infants and young children with refractory epilepsy, including children with Lennox-Gastaut syndrome (LGS), infantile spasms (IS), and other epileptic conditions. The drug produced good therapeutic effects in several forms and etiologies of epilepsy and a large number of children were experiencing complete remission, or greatly reduced seizures. Despite the observed side effects, they tended to be mild and temporary, somnolence, loss of appetite and behavior change being the most frequent ones. These results indicate that topiramate is useful and effective in the manner of management of children who experience frequent incidences of seizure that have not been able to be treated by the superior use of conventional antiepileptic medicines (AE), or AEDs.

Nevertheless, although the immediate effectiveness and tolerance of the topiramate is encouraging, the long-term safety and possible side effects in newborn infants and infants that are extremely young requires further investigations. Research in future needs to concentrate on the long-term effects of topiramate especially on the cognitive development, metabolic functions among other side effects that may arise. However, many uncertainties are still ahead

of topiramate as a treatment to refractory epilepsy in pediatrics particularly in cryptogenic and LGS-related epilepsies.

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