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The efficacy and side effects of topiramate on refractory epilepsy in infants and young children: A multi-center clinical trial

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Summary

Objectives: This study has been conducted to assess the efficacy and safety of topiramate in refractory epilepsies in infants and young children.
Methods: A prospective clinical trial was performed in three tertiary care hospitals, on 47 children aged 6—60 months with refractory epilepsy. Topiramate was added to at least two baseline anti-epileptic drugs. The efficacy was rated according to seizure type, frequency and duration.
Results: Children with refractory epilepsy were classified according to their clinical, neuro-imaging, and neurophysiological profile into infantile spasms (IS) (9 cases, 19%), Lennox—Gastaut syndrome (LGS) (25 cases, 53%) and other epilepsies (13 cases, 28%). Children were also classified into cryptogenic and symptomatic epilepsy. Topiramate was introduced as add-on therapy in a daily dose of 1 mg/kg/day for 2 weeks, followed by increments of 1—3 mg/kg/day at 2-week intervals, up to a maximum of 10 mg/kg/day. After a minimum treatment period of 6 months, 28 (60%) of the children had a satisfactory response (completely seizure free, or more than a 50% seizure reduction). The remaining 19 children (40%) had an unsatisfactory response (50% or less reduction in seizure frequency, no change or increased seizure frequency).

Topiramate appeared to be equally effective in infantile spasms, Lennox—Gastaut syndrome and children with other types of epilepsy, with no significant difference between those with a satisfactory and an unsatisfactory response ($p = 0.089$). There was also no significant difference in response between patients with cryptogenic and symptomatic epilepsy ($p = 0.360$).

Mild to moderate adverse effects, mainly somnolence, anorexia and nervousness, were present in 25 (53%) of children. One of the children developed hypothyroidism.

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Conclusion: Although the long term safety and possible adverse effects of topiramate have not been fully established in infants and young children, this study has shown that it is a useful option for children with frequent seizures unresponsive to standard anti-epileptic drugs.

Introduction

Topiramate is a novel antiepileptic drug (AED) that acts by blocking sodium channels, enhancing GABA-induced influx of chloride, and inhibiting kainite/AMPA glutamate receptors.[1–3]

The clinical efficacy and safety of topiramate has been thoroughly evaluated in adults. It has been shown to be effective as an adjunctive therapy for multiple seizure types including localization-related and primary generalized seizures.[4–6]

Recent reports have demonstrated the efficacy of topiramate in school-aged and older children with generalized and partial epilepsy.[7–10] Topiramate is also effective in the management of Lennox–Gastaut syndrome (LGS) and infantile spasms (IS).[11–16]

There are only a few reports regarding the effectiveness of topiramate in infants and young preschool epileptic children. We therefore designed this prospective multi-center study to assess the safety and effectiveness of topiramate in different types of epilepsy in children between the ages of 6 and 60 months.

Methods

This study was designed to assess prospectively the efficacy of topiramate in infants and young children with refractory epilepsy. A consecutive series of 47 children (27 boys and 20 girls), aged between 6 and 60 months, with refractory epilepsy (defined as recurrent seizures that have failed to respond to trials of at least two AEDs used in combination, despite using the maximum dosage, or dosage resulting in therapeutic drug levels) was identified between January and December 2002. The children were recruited from three tertiary hospitals in Jordan, King Abdullah University Hospital and Princess Rahmah Teaching Hospital in the north and King Hussain Medical Center in Amman. The ethical committees of the three hospitals approved the study.

Patients were selected according to the following criteria: (i) age between 6 months and 5 years; (ii) refractory epilepsy; (iii) currently on at least two AEDs; (iv) absence of progressive neurological disease. Electroencephalograph (EEG) and computerized tomography or magnetic resonance imaging were performed on all patients.

Using seizure diaries, parents or caregivers were asked to record the frequency, type and duration of all seizures. For those with frequent spasms, and absences which were difficult to count, parents were asked to record on a weekly basis the estimated percentage change in seizure frequency, the options being completely seizure free, >50% improvement, no change, <50% improvement, and worsening. Financial restrictions precluded repetition of the EEG.

Seizures were classified into 3 categories: (i) IS based on typical clinical and EEG features (ii) LGS based on clinical (the presence of mixed seizure patterns with some degree of developmental delay or intellectual disability) and EEG (a typical EEG pattern of slow spike wave discharge) features, and (iii) other epilepsies when the first two were excluded. Seizures were also classified by etiology into cryptogenic and symptomatic, five of the nine children with IS having tuberose sclerosis.

After obtaining informed consent, topiramate was started twice daily in a total daily dose of 1 mg/kg followed by 2-weekly increments of 1–3 mg/kg/day until the minimum effective dose was reached (achieved a seizure free outcome), up to a maximum dose of 10 mg/kg at all ages, unless the child was unable to tolerate it.

The 47 children included in the study were followed up for a mean period of 6 months (range 3–10 months). Side effects, blood levels of the concomitant AEDs, liver profiles, EEGs, renal ultrasound and eye examination were monitored in all children. We had no facilities to check topiramate blood levels. Therapeutic responses were recorded as satisfactory if there was a complete remission (seizure free) or more than a 50% seizure reduction, and unsatisfactory if there was a seizure reduction of 50% or less, unmodified seizures, or worsening of seizures. Patients were asked to attend hospital monthly to be examined for possible side effects, or earlier if any problems arose. The collected data were analyzed using Epi Info version 6, and differences between groups were examined by Fisher's exact test.

Table 1 Demographic and baseline characteristics of patients receiving topiramate ($n = 47$).

Attribute	Number and percentage
Age (months)	
Range	6—60
Mean	33
Gender	
Boys	27 (57%)
Girls	20 (43%)
Epilepsy classifications	
Symptomatic	15 (32%)
Cryptogenic	32 (68%)
Infantile spasm	9 (19%)
Lennox—Gastaut	25 (53%)
Others	13 (28%)
Number of background AEDs	
Two AEDs	32
More than two AEDs	15

Results

Forty-seven children entered the study. Their demographic characteristics, diagnoses and seizure classifications are detailed in Table 1.

The response to topiramate is detailed in Table 2, with 60% of the children showing a satisfactory response. Topiramate was discontinued because of side effects in 15 children, because of worsening seizure frequency in 4 (9%), a significant weight loss in 2 (4%), and lack of response in 9 (19%). Although other epilepsies appeared to respond better than LGS to topiramate, the difference was not significant (Fisher's exact test $p = 0.077$), nor was any other differences between groups.

The response of LGS children to topiramate was substantial as 20% had complete remission and another 32% had good response with marked reduction (>50%) in the frequency of their seizures. Four 9 infants with IS became either seizure free or achieved more than a 50% reduction in their seizures frequency, three of them with tuberous sclerosis. In the 13 children with other epilepsies, eight with partial and five with generalized epilepsy, the response to topiramate was encouraging; two became seizure free and nine achieved >50% reduction in seizure frequency.

Table 3 Adverse effects observed during treatment with topiramate ($n = 25$).

Side effects (25 patients)	Number of patients	Percent
Somnolence	13	28
Poor appetite	11	23
Nervousness, irritability and agitation	11	23
Fatigue	9	19
Abdominal pain	9	19
Headache	5	11
Dizziness	5	11
Worsened seizures frequency	4	9
Psychomotor slowing	4	9
Weight loss	2	4
Visual complain	2	4
Memory complain	2	4
Hypothyroidism	1	2

Side effects to topiramate are detailed in Table 3 and were found in 25 (53%) of the patients. The most common side effect was a decrease in appetite and somnolence. One of the patients developed hypothyroidism during the introduction of topiramate. Topiramate had to be withdrawn from four (9%) patients because of worsening seizure frequency and from another two (4%) because of progressive weight loss.

Discussion

This study shows that topiramate is effective and well tolerated in infants and young children with refractory epilepsy. The response is worthwhile in

Table 2 Responses to topiramate according to the clinical types of epilepsy.

Response	LGS ($n = 25$)	IS ($n = 9$)	Others ($n = 13$)	Total ($n = 47$)	Cryptogenic ($n = 32$)	Symptomatic ($n = 15$)
Total remission	5	2	2	9	7	2
>50% improvement	8	2	9	19	14	5
Total satisfactory	13	4	11	28	21	7
≤50% improvement	3	2	1	6	3	3
No response	6	2	1	9	6	3
Worse	3	1	0	4	2	2
Total unsatisfactory	12	5	2	19	11	8

all types of epilepsy, with no significant difference between different clinical types or between cryptogenic and secondary epilepsies.

Similar findings haves reported by Hassan et al. who reported that 34% of children with intractable seizures become seizure free and 39% achieved more than a 50% reduction in seizure frequency.[17] Ritter et al. reported similar findings in children with partial epilepsy, with >50% reduction in symptom frequency in 57%, 14% becoming seizure-free.[18] In children and young adults with refractory partial epilepsy, Coppola et al. achieved seizure free status in 20% and a 50% reduction in seizure frequency in 45%.[8] Biton et al. also reported a substantial response in children with primary generalized epilepsy, 46% having >50% reduction in their seizure frequency compared to the 17% in the placebo control group.[4]

LGS is notoriously difficult to treat, and the response of this group to topiramate was remarkable, 60% achieving a satisfactory response. Sachdeo et al. in a randomized double blind study reported that 30% of LGS had >50% reduction in their seizure frequency compared to 8% in the placebo control group.[14] Similar to the finding in this study, Glauser et al., in an open label trial on LGS, reported that 15% had no more drop attacks and 55% had >50% reduction of their seizure frequency.[19] Coppola et al. and Alva Moncayo et al. also reported a good response to topiramate in LGS.[15,16]

The optimal treatment for IS remains controversial. First-line therapies include adrenocorticotrophic hormone, steroids and vigabatrin. The infants with IS in this study had failed to respond to these medications before topiramate was added, and we achieved a satisfactory response in four of our nine cases. Glauser et al. reported that 45% of his infants with IS become spasm free with topiramate, and concluded that topiramate was a promising drug for the treatment of IS.[11] Thiji et al. and Watemberg also reported a good response to topiramate in children with IS who failed to respond to standard therapy.[12,13] Recent reports concerning the efficacy of topiramate in children with intractable epilepsies included infants and children with IS and LGS. In those reports topiramate therapy was found to be uniformly efficacious and well tolerated in a variety of syndromes although data for infants with IS were not analyzed separately.[7,8,17,20]

In children with partial and generalized refractory epilepsy, there was a satisfactory response to topiramate in 11 of our 13 cases. Previous reports have also shown a good response.[7–10,17,20]

Based on the experience of others, the maximum dosage of topiramate did not exceed 10 mg/kg/day.[7–17] Preliminary data on the pharmacokinetics of topiramate in infants and young children suggest that clearance is linear, with a higher plasma clearance than that reported from older children and adults.[21] It is also recommended that in younger children dosage be adjusted according to response rather than using the absolute topiramate dose. It is therefore possible that higher doses (>10 mg/kg/day) may prove to be more effective in the future.[21]

As shown in Table 3, most of the side effects of topiramate were minor and the drug was well tolerated. Side effects were noted in 53% of the patients, the most common being somnolence, decreased appetite and behavioral changes. Renal stones were not encountered, although as a precaution routine renal ultrasound examinations were performed every 6 months on all patients. Most of the side effects were transient, particularly the somnolence and decreased appetite, which resolved spontaneously or with dose reduction. Nevertheless, topiramate had to be withdrawn in 13% because of seizure worsening and progressive weight loss.

The frequency of side effects in our study is similar to that reported by Ritter et al., who reported that 6% of children discontinued topiramate because of adverse effects and 13% discontinued because of inadequate seizure control. Glauser et al. reported that 71% of their children were continuing topiramate therapy at the last visit.[18,19] Sachdeo et al. reported that when a lower target dose was used (6 mg/kg/day), no patient discontinued topiramate due to adverse events but despite using this lower target dose, 20% of their patients also had weight loss.[14] In comparison with other studies, relatively fewer cognitive side effects (psychomotor delay) have been found. This is likely to be the result of the slow rate of drug introduction (cognitive side effects are reported to be more common with rapid dose titration[22]) and the policy of using the minimum effective dose.

Takeoka et al. reported mild metabolic acidosis (decreased serum bicarbonate) in children on topiramate, presumably related to carbonic anhydrase inhibition, and caution was recommended when topiramate is used in children with conditions that may predispose to acidosis or poor weight gain.[23] We did not routinely screen acid-base balance in our patients. Topiramate therapy had recently been reported to be associated with glaucoma[24] and we performed routine examinations on all our patients at 6-monthly intervals. Two children in our series had visual complaints and were referred to ophthalmologist; they did not have glaucoma. One of our children with LGS developed hypothyroidism. This child was diagnosed with hypothyroidism at the age of 40 months because of psychomotor retardation, 9 months after adding topiramate. Before the introduction of topiramate he received carbamazepine

for 4 months at the age of 15 months then changed to valproate and clonazepam until the age of 31 months when topiramate was added. The relationship between hypothyroidism and topiramate therapy in this child is uncertain, as he was on other AEDs and baseline thyroid function tests were not available.

Although the long term safety and possible adverse effects of topiramate have not been fully established in infant and young children, our study confirms that topiramate is a valuable option for children with high seizure frequency unresponsive to standard AEDs.

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