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An open label trial of topiramate as add-on therapy for Malaysian children with inadequately controlled epilepsy

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Abstract

Objectives: To evaluate the efficacy and safety of topiramate as adjunctive therapy in children with inadequately controlled epilepsy. *Methods:* Children, aged 1-15 years, with inadequately controlled epilepsy were entered into the trial. Topiramate was prescribed at doses of 1- 9 mg/kg/day for 6 months. Primary efficacy variable was the percent reduction in the seizure rate during the maintenance treatment phase. Secondary efficacy evaluation included percentage of patients with ≥50%, ≥75% and 100% reduction in seizure rate and pediatricians' and parental clinical global evaluation. Safety evaluations were performed by monitoring of adverse events and laboratory tests. *Results:* 40 children with a median age of 7 years were recruited. Median Topiramate dosage at endpoint was 5 mg/kg/day. The median percentage reduction in seizure rate was 66 %. Twenty four (60%) had ≥50% seizure reduction, 13 (32.5 %) had ≥75% seizure reduction and 4 (10%) became seizure free. Investigators' global evaluation at endpoint indicated 7 (17.5%) of the children had a good outcome while parental assessment indicated good response in 9 (22.5 %) of the children. The most common adverse events were anorexia (42.5%), somnolence/lethargy (32.5%) and fever/upper respiratory infections (22.5%), but these were largely transient. Four (10%) patients discontinued the study due to poor seizure control and concomitant adverse events.
Conclusion: Topiramate appears to be efficacious and safe in children with a wide variety of refractory seizures.

INTRODUCTION

Epilepsy is a common disorder in children. While the long term prognosis of most children are good, up to 20% are considered to be refractory to treatment, even in developed countries with many approved antiepileptic drugs (AEDs) and several non-pharmacologic options available.[1]

Topiramate is a novel AED with multiple modes of action. Randomized controlled studies have demonstrated efficacy of topiramate as adjunctive therapy in children with partial seizures[2], generalized tonic-clonic seizures[3] and Lennox-Gastaut syndrome.[4] A study in Asian adult patients with partial epilepsy demonstrated efficacy and safety, quoting lower doses than those recommended in Western countries.[5] This study was undertaken to assess the efficacy, safety and doses required to attain seizure control in Malaysian children with diverse forms of severe epilepsy.

METHODS

Study design

This was a multicentre, open-label trial with a one month baseline (screening) phase and a 6 months treatment phase conducted in the Paediatric Departments of Hospital Universiti Kebangsaan Malaysia, Institut Paediatrik Kuala Lumpur and Hospital Pulau Pinang. These hospitals served as the main tertiary referral centers for children with poorly controlled seizures.

Patients

All consecutive children, aged 1-15 and who weighed at least 11 kg, with inadequately controlled epilepsy (partial onset with or without secondary generalization, generalized tonic clonic, myoclonic or absence seizures, drop attacks) were

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recruited for the study. Patients who were more than three years old had to have at least two years' history of epilepsy, while those less than three years of age needed to have at least six months of epilepsy at the time of entry into the trial. Inadequate control was defined as at least four seizures per month while maintained on one or more appropriate AEDs, and if there was potential for further improvement in seizure control based on clinical judgment.

Criteria for exclusion from the study included benign Rolandic epilepsy, those who did not have epilepsy (pseudoseizures or seizures due to a metabolic disturbance or infection), those who had less than four seizures during the baseline phase, progressive or degenerative disease (including arteriovenous malformation), history of status epilepticus within 3 months of baseline, malignancy, clinically significant abnormal baseline laboratory parameters, recent treatment of an experimental drug within 30 days of baseline, previously treated with topiramate, use of acetazolamide or medication associated with nephrolithiasis.

The trial was conducted in accordance with the International Committee on Harmonization of Good Clinical Practice guidelines. Written informed consent was obtained from the legal guardian before study related procedures were initiated. Ethics approval was obtained from the respective hospital ethics committees.

Treatment

The initial dose of topiramate was 1 mg/kg/day for one week, followed by an increment to 3mg/kg/day in the second week, and thereafter increments of 1 mg/kg/day were made weekly, until minimum effective or maximum tolerated dose was achieved. At the investigator's discretion, fortnightly increment could be performed to reduce the onset or persistence of adverse effects. Most patients were expected to achieve efficacy at a dose of 5-9 mg/kg/day. If doses higher than 9 mg/kg/day were judged to be required and the patient was tolerating the medication well, the investigator had to contact the sponsor for approval. Topiramate was administered initially as a single evening dose in the first week, and twice daily thereafter. At the investigator's discretion, other AEDs that the patient was on could be reduced or withdrawn if good seizure control was achieved.

Assessment of efficacy

Patients' caregivers were instructed to keep a diary and record the date and time of each seizure and a brief description of the seizure type throughout the baseline and core phase. Monthly visits were done, and seizure data were transcribed onto the case report form (CRF) at each visit.

It was found very early on in the study that many patients were being titrated on a fortnightly rather than a weekly basis, hence the maintenance dose of topiramate for the majority of patients was reached after two or three months rather than the anticipated one month. The primary efficacy variable was thus taken as the percent reduction from baseline in average monthly seizure frequency during the maintenance treatment phase (arbitrarily taken as the last three months of treatment). Secondary efficacy evaluation included percentage of patients with $\geq$50%, $\geq$75% and 100% (seizure free) reduction rate. Investigators' and parental global evaluation of improvement at the end of the treatment phase was also performed, using a 5-point scale (worse, no improvement, minimal, moderate and marked improvement).

Safety data

Adverse event data were collected by interviewing patients or caregivers at each study visit. A treatment emergent adverse event (TEAE) was defined as an adverse event that was either new in onset or aggravated in severity during the treatment phase. Events were graded by severity and evaluated by the investigator as to the probability of relationship to treatment and whether the event persisted. Only events that were judged to be certainly, probably or likely to be related to topiramate were considered for analysis.

Clinical laboratory tests (full blood count, glucose, creatinine, liver enzymes, carbon dioxide and bicarbonate) were performed at baseline and at end of treatment phase. Female patients who had attained menarche were required to have a urine pregnancy test.

Statistical method

Statistical analysis was conducted on an intent-to-treat basis and considered all data from both the baseline and maintenance treatment phase. Categorical data were summarized in contingency tables and subjected to chi-square (or Fischer exact test) analysis. Comparison of continuous

data before and after treatment was done by means of Wilcoxon signed ranks test where appropriate. All tests were interpreted at the 5% significance level (two-tailed).

RESULTS

Forty patients, with a median age of 7 years (range 2-15), were enrolled. Twenty-one (52.5%) were male and 19 (47.5%) were female. There were 19 (47.5%) Malay, 19 (47.5%) Chinese and 2 (5%) Indian patients. Fifteen (37.5%) children had motor deficits, while 35 (87.5%) children had underlying behavioral or cognitive problems.

The median duration of epilepsy in these patients was 4 (range 1-13) years. Based on the ILAE classification of epilepsies and epileptic syndromes, 22 had localization related epilepsy (15 symptomatic secondary to cerebral malformations or previous infections/ perinatal asphyxia, 7 cryptogenic) while 18 had generalized epilepsy (4 severe mycoclonic epilepsy of infancy, 2 Lennox Gastaut syndrome, 2 myoclonic-astatic epilepsy and the rest were symptomatic epilepsies that could not be defined). The median monthly seizure frequency for all seizure types in the baseline phase was 43 (range 5-2564). Partial seizures occurred in 22 patients (median monthly frequency 29, range 1-1300), myoclonic seizures in 12 patients (median monthly frequency 100, range 7-475) and other forms of generalized seizures occurred in 19 patients (median monthly seizure frequency during baseline 22, range 5-2444). At baseline, the median number of AEDs used was 2 (range 1-4). Seven (17.5%) patients were on one AED, 24 (60%) on two AEDs and 9 (22.5%) on three or more AEDs. The background AEDs included carbamazepine (18 patients), valproic acid (30), clonazepam (15), lamotrigine (16), gabapentin (1), phenobarbitone and phenytoin (2 patients each).

Four (10%) of the patients discontinued the study between visits 3-6 due to poor response to therapy and concomitant side effects (2 somnolence, 1 anorexia and 1 behavior problems). One patient died during the trial, due to gastrointestinal hemorrhage from a gastrostomy tube, which was judged to be unrelated to topiramate. All 40 patients were evaluated on an intent to treat basis. For primary efficacy endpoint, the median percent reduction in seizure rate from baseline was 66%. Twenty-four (60%) patients had a >50% reduction, 13 (32.5%) had a >75% reduction and 4 (10%) were seizure free. Seven (17.5%) reported an increase in seizure frequency. There were no differences in seizure reduction rates comparing seizure type (Table 1). The global evaluation scale indicated moderate or marked improvement in 7 (17.5%) and 9 (22.5%) patients by investigator and parental reporting respectively (Table 2).

The median dose of topiramate was 5 mg/kg day (range 2-10 mg/kg/day), and was similar for all seizure types. There was no change in the median number of concomitant AEDs used at baseline and at the end of the treatment phase (Wilcoxon signed rank test, p=0.705). At the end of the treatment phase, 31 (77.5%) patients opted to continue topiramate but the figure fell to 21 (52.5%) at one year post trial. Reasons for discontinuing treatment at one year were inadequate seizure control (5 patients), with concomitant unacceptable side effects in another 5 patients.

Table 1: Percentage of patients with ≥50%, ≥75% and 100% reduction from baseline for different seizure types

Percentage reduction of average monthly seizure rate	Seizure type*		
	Partial n=22	Myoclonic n=12	Other Generalised n=19
No change	5 (22.7)	3 (25.0)	5 (26.3)
Increased frequency	5 (22.7)	2 (16.6)	4 (21.0)
≥50% reduction	12 (54.4)	7 (58.3)	10 (52.6)
≥75% reduction	10 (45.5)	7 (58.3)	9 (47.4)
100% (seizure free)	6 (27.3)	2 (16.6)	3 (15.8)

Figures in parentheses indicate percentage

* Each patient can have more than one seizure type

Table 2: Investigator and parental global evaluation ratings at the end of treatment phase

Rating	Parent	Investigator
Worse	12 (30.0)	5 (12.5)
No improvement	10 (25.0)	20 (50.0)
Minimal improvement	9 (22.5)	8 (20.0)
Moderate improvement	8 (20.0)	7 (17.5)
Marked improvement	1 (2.5)	0 (0)

Figures in parentheses indicate percentage

Table 3: Incidence of treatment emergent adverse events (TEAEs) during study period

Type of TEAEs*	No. of patients affected	No. persisted
Somnolence/lethargy	13 (32.5)	3 (7.5)
Anorexia	17 (42.5)	1 (2.5)
Weight loss	5 (12.5)	2 (5)
Memory/learning problems	6 (15)	3 (7.5)
Behavior problems	5 (12.5)	4 (10)
Fever/URTI#	9 (22.5)	1 (2.5)
Gastrointestinal problems (constipation, diarrhoea,etc)	6 (15)	1 (2.5)

Figures in parentheses indicate percentages
* Each patient may have more than one TEAE
# Upper respiratory tract infections

TEAEs were reported in 34 (85%) patients. The most commonly reported TEAEs were anorexia, somnolence and fever; the latter often associated with upper respiratory infections (Table 3). However, these largely resolved and the rate of persistent events did not exceed 10%. Three children (7.5%) had intermittent unexplained fever that were judged to be probably related to topiramate therapy but two were transient and none required withdrawal of therapy. All these children were ambulant and physically active, and the febrile episodes occurred when a topiramate dose of 3 mg/kg/day was achieved. Behavior problems or learning difficulties were more likely to persist than other TEAEs. All eleven patients with reported behavioral or learning problems had a baseline history of such problems compared to 83% of those who did not have such TEAEs, but the difference was not statistically significant (p=0.306). Significant weight loss (defined as more than 10% of baseline weight at any time during the treatment phase) occurred in 5 (12.5%) patients; however there were no withdrawal from the study because of weight loss. No reports of glaucoma were noted.

There were no clinically significant changes in laboratory values from baseline to the final visit.

DISCUSSION

The study shows that topiramate adjunctive therapy improves seizure control in this group of children with severe epilepsy, many of whom were on multiple AEDs and had concomitant neurologic, cognitive or behavioral problems. Approximately half our patients experienced a $\geq$50% reduction in seizure rate, which is comparable to other studies on generalised[3,6] or partial[2,5-7] seizures that used a similar trial duration. Other studies[8,9] that reported a lower seizure reduction rate were pragmatic trials with a longer duration of follow up. Given that our cohort of patients had long standing refractory epilepsy, the period of follow up is important when comparing efficacy. Three quarters of our patients opted to continue topiramate at the end of the six months' trial, but the figure had fallen to half

after one year. This trend is similar to pragmatic studies[6,8,9] of children with diverse seizures and epilepsy syndromes. However, the reasons for discontinuation were different. While all our patients withdrew because of lack of efficacy (half of them had concomitant adverse effects), the main reason for withdrawal in others[6,8] were due to unacceptable adverse events. Overall improvement using the global evaluation scale was 22.5%, lower than those reported by other studies[2-5] which looked at evaluation of seizure severity improvement alone. The discrepancy between the seizure reduction rate and global evaluation scale in this study was because the latter also took into account other parameters (changes in alertness, level of interaction and responsiveness, and ability to perform activities of daily living) that might impact on the patients' daily lives.

The incidence of TEAEs in our study was comparable to others, with the most common events being somnolence, anorexia or weight loss, behavior or learning problems and fever/ upper respiratory infections. It was not clear if these were related to the rapid dose escalation regime or type of concomitant AEDs used. There is still controversy as to whether adverse events are attributable to rapid titration.[10] Many of these TEAEs were self -limiting, and none resulted in patient withdrawal from the study during the treatment phase. While this was reassuring, the fact that behavioral or cognitive problems tended to persist is in keeping with postmarketing experience.[11] This might discourage patients from continuing topiramate long term, even if the patients achieve reasonable seizure control. Gerber *et al*[10] reported that a previous history of behavioral problems was an important predisposing factor. The large number of patients in our study with premorbid behavioral or cognitive problems precluded meaningful analysis. Fever has been described as an important adverse event in summer or hot regions, presumably due to the carbonic anhydrase inhibition effect of topiramate resulting in decreased sweating and problems with thermoregulation.[12] Three of our patients probably had this problem, although these were self limiting and did not require changes in topiramate dosing. Nevertheless, in a tropical climate setting like ours, patients (especially those who are ambulant and physically active) should be warned about such potential problems.

The median dose used in this study was 5 mg/ kg, comparable to that used by others.[2,3,7,10] Some have suggested that children might tolerate higher doses than that recommended, especially in younger children[6,9,13] and specific epilepsy syndromes.[4,6] However, given the high incidence of adverse events in this study, the use of higher doses needs to be approached with caution. Dose escalation beyond the recommended range will need to be individualized and carefully monitored, perhaps at a slower rate than the weekly titration rate originally recommended in this study.

In conclusion, topiramate appears to be efficacious as adjuvant therapy in children with poorly controlled partial or generalized seizures. Although there was no reduction of concomitant AEDs and the one-year post trial experience shows only half of the patients opted to continue topiramate therapy, the drug remains an important armamentarium for therapy of refractory seizures in children.

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