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An open label trial of topiramate as adjunctive therapy in Asian patients with refractory partial epilepsy

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Abstract

Objectives: The study evaluated the efficacy and safety of topiramate as adjunctive therapy in patients with refractory partial seizures with or without secondarily generalization. *Methods:* A historical assessment of patients was performed before study. Topiramate was prescribed at target dosages of 200 – 1600 mg daily for 6 months. Primary efficacy variable was the percent reduction in the average monthly seizure rate in the core phase relative to the retrospective baseline phase. Secondary efficacy evaluation included percentage of patients with ≥ 50%, ≥ 75% and 100% reduction in seizure rate and clinical global evaluations. Safety evaluations were performed by monitoring of adverse events, vital signs and laboratory tests. *Results:* 103 patients with a mean age of 31 years were recruited. Median topiramate dosage at endpoint was about 300 mg daily (range: 100mg – 1200 mg). Fifty-three percent of patients had ≥ 50% seizure reduction, 31% had ≥ 75% seizure reduction and 12% became seizure free. Investigators' global evaluation at endpoint indicated that 86% of patients improved compared to baseline, while patients' own assessment of the treatment indicated good to excellent response in 53% of patients. The most common adverse events were central nervous system related.
Conclusions: Topiramate appeared to be efficacious and safe in patients with refractory partial seizures.

INTRODUCTION

Epilepsy is a common neurological disorder, affecting approximately 50 million people worldwide. It has been estimated that more than 5 million people experience at least one seizure per month and almost three-quarters of these people receive no treatment for their seizures.[1] Even in developed nations with more than 20 approved anti-epileptic drugs (AEDs) and several non-pharmacological options available, up to 30% of patients are still refractory to treatment.[2]

Topiramate, a sulfamate-substituted derivative of d-fructose, is a novel AED indicated for use as an adjunctive therapy in adults and children with partial seizures, seizures associated with Lennox-Gastaut syndrome and generalized tonic-clonic seizures. Randomized controlled studies suggested that it is one of the most potent new generation AEDs.[3] The efficacy and safety of topiramate as adjunctive therapy in refractory partial epilepsies have been studied extensively studied in the West and recently in Korea.[4-10] All these studies demonstrated significantly higher efficacy of topiramate compared to placebo. To our knowledge, efficacy and safety of topiratmate have not been studied in a multinational trial in other Asian patients.

METHODS

Study design

This was a multi-center, open-label trial with an 2 months retrospective baseline phase and 6 months core phase conducted in Singapore, Thailand, Philippines, Hong Kong and Indonesia.

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Patients

Male and female epilepsy patients, aged 12 years or older, who had at least 2 years history of partial seizures with or without secondary generalization were recruited. These patients were judged by the investigators to have inadequate response to one or two of the following AEDs at baseline phase: phenytoin, carbamazepine, valproic acid, phenobarbital, and primidone. Patients were required to provide documentations that demonstrated the frequency and type of seizure during the eight-week retrospective baseline phase. Female patients had to be practicing an acceptable method of birth control during core phase.

Reasons for exclusion from the study included progressive neurologic disease, history of status epilepticus within 3 months of baseline, significant acute or chronic confounding disease, malignancy, history of serious psychiatric disorder, nephrolithiasis, clinically significant abnormal baseline laboratory parameters, and poor compliance with therapy. Additional exclusion criteria included recent treatment with an experimental drug within 30 days of baseline, previously treated with topiramate, use of acetazolamide, and a history of an inability to take medication or maintain a seizure calendar, independently or with assistance.

The trial was conducted in accordance with International Committee on Harmonization of Good Clinical Practice (ICH-GCP) guidelines. Written informed consent was obtained from the patient or legally authorized representatives of each patient before study-related procedures were initiated.

Assessment of Efficacy

Patients or patients' caregiver kept a diary and recorded the date and time of each seizure and a description of the seizures type. Seizure data were transcribed onto the appropriate case report form. The patient or their caregiver were instructed on the type of recordings to perform and were requested to ask those witnessing the events for descriptions.

The primary efficacy variable was the percent reduction in the average monthly seizure rate in the core phase relative to the retrospective baseline phase. Data from the last three month of the core phase was used for the primary efficacy assessment. Secondary efficacy evaluation included percentage of patients with ≥ 50%, ≥ 75% and 100% (seizure free) reduction in seizure rate, investigator's global evaluation of improvement, and patient's overall assessment of study medication. Rating for the global evaluations were as follows: investigator's evaluation of improvement: marked (5), moderate (4), minimal (3), none (2), worse (1); patient's assessment of medication: excellent (4), good (3), fair (2), poor (1).

Safety Data

Adverse events were reported by the patients and/or caregiver at each visit during the core phase, and were coded using modified World Health Organization adverse reaction terminology. A treatment-emergent adverse event (TEAE) was defined as an adverse event that was either new in onset or aggravated in severity or frequency during the core phase. Events were graded by severity and evaluated by the investigator as to probability of relationship to treatment. Clinical laboratory tests (including hematology and blood chemistry), and vital signs were performed at baseline and then two times during the 24-week core phase.

Treatment

The initial dose of topiramate was 50 mg/day for one week followed by increments of 50 mg/week, until maximum effective or maximum tolerated dose was reached. At the investigator's discretion, the dose may be increased by 25 mg/d/week. If the doses needed to be increased above 400 mg/d, it was titrated at a rate of 50 – 100 mg/d/week; again, a 25 mg/d/week titration rate was used if necessary. The total daily dose of topiramate would not exceed 1600 mg. Topiramate was administered in a twice-a-day regimen. In order to improve a patient's tolerability at higher doses, the daily dose frequency was increased. In addition, patients controlled at lower doses were maintained on a once daily regimen, the medication was taken at bedtime.

Statistical Method

The statistical analysis was conducted on an intent-to-treat basis and considered all data from both the retrospective baseline and the core phase. Since this was an open-label study, only descriptive analyses were performed. All descriptive statistics were tabulated. Categorical data were summarized in contingency tables with frequencies and percentages. The comparison of data before and after treatment was done by means of paired t-tests or rank-sum tests as appropriate. All statistical tests were interpreted at the 5% significance level (two-tailed).

RESULTS

Patient characteristics.

One hundred and three patients, with a mean age of 31 years. (range 12 to 53 years) were enrolled. Fifty-four patients (52%) were female and 49 patients (48%) were male. Nine per cent of patients had simple partial seizures, 75% had complex partial seizures while 48% had partial seizures with secondarily generalized tonic-clonic seizures. The median topiramate dose per patient at endpoint was 300 mg/day (range 100 mg/day to 1200 mg/day), while the mean dose per patient at endpoint was 411 ± 290 mg/day. Seventeen percent of patients were receiving one concomitant AED, while the remainder received two or more concomitant AEDs. The demographic and patient characteristics are shown in Table 1.

Efficacy

All 103 patients were evaluated on an intent-to-treat basis. For primary efficacy endpoint, the median percent reduction in the average monthly seizure rate in the last three months of the core phase compared to the retrospective baseline phase was 56% ($P<0.001$). Secondary efficacy evaluation showed that there were 53% of patients with a ≥50% seizure reduction, 31% with a ≥75% seizure reduction and 12% with 100% seizure reduction (seizure free). The investigators' global evaluation of improvement on 91 patients indicated that 86% showed an improvement over baseline. The improvement was marked in 25 patients (28%), moderate in 34 patients (37%), minimal in 19 patients (21%), none in 11 patients (12%), and worse in 2 patients (2%). The patients' overall assessment of treatment on 91 patients indicated that 53% reported good to excellent. The assessment was excellent in 13 patients (14%), good in 35 patients (39%), fair in 29 patients (32%), poor in 14 patients (15%).

Safety

The most common TEAEs occurring during the core phase are shown in Table 2. Central nervous system events were the most frequent category including somnolence, anorexia, dizziness, paresthesia, amnesia, asthenia and nausea. Most TEAEs *were* classified as mild (67%) or moderate (28%) in severity. One patient experienced a serious adverse events (encephalitis) which was considered by the investigator to be unlikely related to topiramate. Seven patients (7%) had to stop topiramate and were withdrawn from the study due to adverse events (Table 3). There were no clinically noteworthy abnormal laboratory findings in biochemical and hematological tests. Similarly, there were no clinically significant changes in vital signs.

Weight loss

All patients in the study reported some degree of weight loss at endpoint versus baseline, with the greatest amount of weight loss occurring in subjects with highest pretreatment weight. In this study, the mean weight loss was 3.1 kg ($p=0.03$) (Table 1). However, no patients withdrew from the study because of complaint of weight loss.

DISCUSSION

Topiramate, a sulfamate-substituted derivative of d-fructose, is a novel AED possessing the following mechanisms of action: (1) modulation of voltage-dependent sodium ion channels; (2) enhanced gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; and (3) blockade of the kainate/AMPA receptor subtype of the excitatory glutamate-mediated neuro-transmission

Several double-blind trails in the West have shown the efficacy of topiramate as adjunctive therapy in adult patients with refractory partial seizures, with or without secondary generalization.[4-9] In addition, a meta-analaysis of all randomized controlled trials available at that time involving lamotrigine, gabapentin, zonisamide, tiagabine, vigabatrin, and topiramate indicated that topiramate had the highest efficacy in seizure reduction in patients with partial seizures.[3] More recently, a double-blind, placebo-controlled Korean study [10] in patients with partial seizures also confirmed a similar efficacy of topiramate compared to Western data.[11-12]

To our knowledge, the current study is the first multinational study on topiramate conducted in Asian patients. The design of this study differed from the Western and Korean studies in that ours was an open-label non-comparative design. There was no minimum baseline seizure rate for subject inclusion; the only criterion in this respect was that patients must be receiving other AED(s), and were still suboptimally controlled in the clinical judgement of the investigators. The other main difference was that the dose titration in this study was lower and slower than the previous Western studies, although it was similar to the Korean study.

Table 1: Patient characteristics

Parameter	n = 103
Sex (Male : Female)	49:54
Age (years), mean (SD)	31 (10)
Weight (kg), mean (SD). Baseline	58 (16)
Weight (kg), mean (SD). Endpoint	54 (13)*
Baseline average monthly seizure rate	
Mean (SD)	13 (20)
Seizure types	
Simple partial	9 (9%)
Complex partial	77 (75%)
Secondarily generalized tonic-clonic	49 (48%)
Concomitant AED(s) at baseline	
One AED	n = 17
CBZ	
PHT	
VPA	
PBT	
Two AEDs	n = 43
CBZ/CLN	
CBZ/GBP	
CBZ/LMG	
CBZ/PBT	
CBZ/CLB	
PHT/VPA	
PHT/PBT	
PHT/CLB	
PHT/CBZ	
VPA/CBZ	
VPA/CLN	
VPA/LMG	
Three AEDs	n = 42
CBZ/CLN/PHT	
CBZ/CLN/VPA	
CBZ/PBT/CLB	
CBZ/PHT/CLN	
CBZ/LMG/PBT	
PHT/CLB/CBZ	
PHT/PBT/CBZ	
PHT/CBZ/GBP	
PHT/VPA/CBZ	
PBT/GBP/LMG	

*Statsitically significant different versus baseline, p = 0.03.
CBZ, carbamazapine; PHT, phenytoin; PBT, phenobarbitone; VPA, valproate; PRM, primidone; GBP, gabapentin; LMG, lamotrigine; CLB, clobazam; CLN, clonazepam;

Table 2: Treatment-emergent adverse events (TEAEs) reported in more than 5% of the subjects

Adverse events	n = 103
Somnolence	42%
Anorexia	34%
Dizziness	15%
Headache	11%
Paresthesia	10%
Amnesia	10%
Nausea	9%
Weight loss	9%
Asthenia	9%

The mean topiramate dose at endpoint was 411 ± 290 mg. In the Korean study, the mean dose was 448.9 ± 170.7mg. It was not possible to obtain a mean dosage for the Western studies because four of these studies used fixed doses (i.e., 400, 600, 800, 1,000 mg). The current product labelling for topiramate indicates a usual daily dose of 200-400 mg for partial and generalized seizures in adults, although individual patients have received doses as high as 1600 mg/day. Therefore, the dose seen in this study was within previously reported doses.

In this study, the median percentage seizure reduction of 56% was fairly similar to the Korean study of 51.3%, though appeared to be higher than the pooled data from the six Western studies (Table 4). Similarly slightly higher % of subjects in this study reported ≥50%, ≥75% and 100% seizure reduction compared to the Korean and the Western studies (Table 4). A probable reason for the higher efficacy rates observed in this study is methodological in that the calculation of seizure reduction was performed using the last three months of the core phase compared to the retrospective baseline phase, whereas in the Korean and Western studies, the calculation was performed using the entire core phase. Indeed, in the Korean study, it was seen that when the calculation was performed using only the last 8 weeks of the core phase, the seizure free rate was twice as high compared to if the entire 18-week core phase was used (Table 4). This upward trend in efficacy is expected as subjects achieved their optimal doses after the titration phase and have their doses individually adjusted to clinical effects. Overall, the current study indicated that topiramate appeared to be as effective in other Asian populations as in Koreans and Western populations.

Western data typically report central nervous system related AEs as being most frequent, e.g., somnolence, dizziness, headache, psychomotor slowing, and speech disturbance (Table 5). On the other hand, the Korean study reported that while non-specific central nervous system related AEs were the commonest, specific GI-related AEs like anorexia, nausea and abdominal discomfort/pain were much more common compared to Western data. In fact nausea and abdominal discomfort/pain were not reported in Western data. In the current study, the top three AEs in terms of incidence were somnolence, anorexia, and dizziness (Table 5). While nausea was reported, it was at half the incidence vis-à-

Table 3: Adverse events that resulted in premature withdrawal from the study

Adverse events[a]	Severity	Relationship to topiramate (as judged by the investigators)
Increased appetite	Mild	Possible
Insomnia	Mild	Possible
Insomnia	Moderate	Possible
Somnolence	Moderate	Probable or likely
Somnolence	Marked	Probable or likely
Coughing	Mild	Possible
Dry skin	Mild	Possible
Skin rash	Marked	Probable or likely
Dizziness	Marked	Certain
Decreased libido	Marked	Probable or likely
Abnormal thinking	Marked	Certain

[a] Refers to number of events, not number of subjects

Table 4: Comparison of Western, Korean and current studies in topiramate efficacy

	Current study	Korean study[10]	Western studies[11-12]
Median percentage seizure reduction	56	51.3	44
Seizure reduction			
ž50%	53	50.6	43
ž75%	31	Not determined	21
100%	12	7.9[a], 16.7[b]	5[a]

[a] Through-out the entire 18-week double-blind phase
[b] During the 8-week stabilization phase

Table 5: Comparison of Western, Korean and current studies in topiramate adverse events

	Current study[a]	Korean study[a]	Western studies[b]
Somnolence	42%	19.8%	29%
Anorexia	34%	20.9%	10%
Dizziness	15%	21.0%	25%
Headache	11%	11.0%	27%
Paresthesia	10%	Not reported[c]	11%
Amnesia	10%	6.6%	12%
Nausea	9%	16.5%	Not reported[c]
Weight loss	9%	8.8%	9%
Asthenia	9%	5.5%	15%
Abd. Discomfort/pain	Not reported[c]	20.9%	Not reported[c]
Psychomotor slowing	Not reported[c]	8.8%	13%
Speech disturbance	Not reported[c]	9.9%	13%

[a] Treatment-emergent adverse events (TEAEs) reported in more than 5% of the study subjects
[b] Data colleceted on more than 2000 patients treated with topiramate in clinical studies for up to 7 years.
[c] "Not Reported" is inclusive of AE with incidence of -5%.

vis Korean data. Abdominal discomfort/pain was not reported at all. Interestingly, psychomotor slowing and speech disturbance was not reported at all as well. It appears that except for the lack of psychomotor slowing and speech disturbance the pattern of AEs seen in this study corroborates with the Korean study, i.e., a higher incidence of gastrointestinal system related symptoms vis-à-vis Western data. Weight loss was reported in this study at similar incidence as the Korean and Western data. In our study, 7% of subjects stopped the trial prematurely because of AEs (Table 3). In comparison, the dropout rate was 7.7% of the subjects in the topiramate arm in the Korean study. The AEs that led to the dropout in both studies were fairly similar and mostly central nervous system in nature.

In conclusion, the current study indicates that topiramate appeared to be effective and safe as add-on therapy in refractory partial seizures in Asian patients. The incidence of AEs had a slightly different profile from Western data, and was more in line with the Korean profile, i.e., and a higher incidence of gastrointestinal system related symptoms. None of our subjects developed nephrolithiasis during the study. There were no biochemical or hematological abnormalities, nor any clinically significant changes in vital signs. Only seven subjects (7% of total subjects entered) stopped the trial prematurely due to AEs.

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