Effect of Topiramate on Intractable Seizures in Taiwanese Children

Sung-Tse Li[1], Ein-Yiao Shen[1,2], Nan-Chang Chiu[1], and Che-Sheng Ho[1]

Abstract- We performed a prospective study to evaluate the effect of topiramate as an adjunctive therapy in Taiwanese children with intractable partial epilepsy and generalized epilepsy. Thirty children aged from 2 to 16 years (8.5±3.8 years) were enrolled in this study. Eighteen children (60.0%) had partial epilepsy, and 12 children (40.0%) had generalized epilepsy. These children were experiencing more than one seizure per month even under a stable antiepileptic regimen treatment. Topiramate was begun at 1 mg/kg·day, and the dosage was raised by 1 mg/kg·day each week. Titration continued for 4 weeks or more. The maximal dosage was 10 mg/kg·day. In children with partial epilepsy, six children (33.3%) achieved ≥ 50% frequency reduction, while eight children (44.4%) achieved a seizure-free state. In children with generalized epilepsy, including infantile spasms, four children (33.3%) achieved ≥ 50% frequency reduction, while five children (41.7%) achieved a seizure-free state. The most common adverse effect was poor appetite (10.0%). No idiosyncratic reactions to topiramate were found. Only one patient discontinued topiramate because of central hyperventilation. Topiramate can be used as an adjunctive antiepileptic drug for intractable epileptic children in Taiwan.

Key Words: Topiramate, Intractable epilepsy, Epileptic therapy, Children

Acta Neurol Taiwan 2004;13:59-63

INTRODUCTION

The incidence of epilepsy in pediatric population is estimated to be about 0.5% to 1%, and it mostly occurs during infancy and childhood[1]. However, about 25% of children are characterized as being refractory to traditional therapy[2]. Topiramate is a new potent antiepileptic drug with multiple mechanisms of action. Among its mechanisms of action include blockade of voltage-dependent sodium channels, enhancement of γ-aminobutyric acid (GABA)-mediated neurotransmission, and inhibition of kainate/AMPA glutamate, an excitatory amino acid receptor[3-5]. Initially, topiramate was indicated for adjunctive therapy in adult patients with partial-onset seizures that were not under adequate control with traditional antiepileptic drugs[6-12]. Subsequently, topiramate as adjunctive therapy has been used in children with refractory partial-onset seizures with or without generalized seizures[13]. Its efficacy and safety have further been assessed in children with gener-

From the Departments of Pediatrics, [1]Mackay Memorial Hospital, Taipei; [2]Taipei Medical University-Municipal Wan-Fang Hospital, Taipei, Taiwan.
Received, May 16, 2003. Revised June 18, 2003.
Accepted January 15, 2004.
Reprint requests and correspondence to: Nan-Chang Chiu, MD. Department of Pediatrics, Mackay Memorial Hospital, No. 92, Sec. 2, Chung Shan N. Road, Taipei, Taiwan.
E-mail: ncc88@ms2.mmh.org.tw

alized tonic-clonic seizures[14], even severe treatment-resistant seizures like infantile spasms[12,15,16] and Lennox-Gastaut syndrome[17,18]. We collected 30 children with refractory seizures, including partial seizures, generalized tonic-clonic seizures, infantile spasms, and other seizure types, to determine the efficacy and safety of topiramate therapy for these kinds of patients in Taiwan.

PATIENTS AND METHODS

The study population included 30 patients with refractory epilepsy who were enrolled between July 2000 and June 2002. There were 16 boys and 14 girls aged from 2 to 16 years (8.5±3.8 years), and who weighed from 3.9 to 68 kg (25.9±14.5 kg). Inclusion criteria required patients to be more than 1 year of age and to have been on a stable antiepileptic drugs (AEDs) regimen, but to still have one or more seizures every month even with the antiepileptic drug level within therapeutic levels.

An electroencephalogram was performed in all patients before topiramate therapy. Seizures were classified according to the recommendations of the International League Against Epilepsy as partial, generalized, or others [19-21].

Before using topiramate, the possible adverse effects and any possible complications were fully explained to the family. Topiramate therapy was begun at 1 mg/kg·day, and the dosage was raised by 1 mg/kg·day each week. The titration rate was reduced if the dose was not tolerated, or if somnolence or weight loss developed. After 4 weeks of titration, topiramate reached a therapeutic dosage. If seizure frequency did not exhibit a ≥ 50% reduction, the dose was increased until the reduction rate was ≥ 50% or to a maximal 10 mg/kg·day. If a child weighed more than 40 kg, we started topiramate therapy at 50 mg/day initially. The dosage was increased by 50 mg each week in the following 3 weeks until it reached 200 mg/day. During the titration period, the dosage of background antiepileptic drugs remained unchanged. Patients were monitored and evaluated during weekly visits and assessed either in person or by telephone. Seizure frequencies before and after topiramate therapy were compared using the Wilcoxon signed rank test (SPSS 9.0 for Windows, 1998, Chicago, Illinois, USA). A value of $p < 0.05$ was considered significant.

RESULTS

In these 30 children, 18 patients (60.0%) had partial epilepsy, and 12 patients (40.0%) had generalized epilepsy. The latter included 6 patients (20.0%) with generalized tonic-clonic epilepsy, four patients (13.3%) with infantile spasms, one patient (3.3%) with absence epilepsy, one patient (3.3%) with myoclonic epilepsy. These patients were regularly followed-up monthly at our outpatient clinics. Before topiramate was administered, these patients had received other AEDs for at last 3 months. Table 1 shows how many and what kinds of AEDs were used as background drugs. Six patients (20.0%) took only one AED before topiramate was prescribed, 24 patients (80.0%) took more than one AED as background drugs. Valproic acid was the most common background AED, followed by carbamazepine. Background AEDs were given continuously throughout the entire titration period. After reaching a therapeutic dosage, two patients stopped one of their other AEDs: one discontinued lamotrigine and the other discontinued phenobarbital. No patient had achieved topiramate monotherapy by the end of stabilization.

Of the 30 patients enrolled in this study, 29 patients had at least a 1-month titration period. One patient

Table 1. *Background antiepileptic drugs of 30 children before topiramate therapy*

Background AED	Patient no.	%
Name of background AED		
Valproic acid	22	73.3
Carbamazepine	21	70.0
Vigabatrin	14	46.7
Phenobarbital	8	26.7
Phenytoin	6	20.0
Lamotrigine	6	20.0
Clonazepam	2	6.7
Number of background AED		
One AED	6	20.0
Two AEDs	14	46.7
Three AEDS	7	23.3
More than three AEDs	3	10.0

AED: antiepileptic drug

stopped topiramate due to adverse effects. The patient developed central hyperventilation syndrome after topiramate therapy, and ceased after discontinuing the drug.

Figure 1 shows the topiramate dosage in children of this study. The mean dosage of topiramate during stabilization was 5.0±2.0 mg/kg·day. The most common dosage was 4-5 mg/kg·day. Reductions in the rate of seizure frequency for partial and generalized epilepsy were 67.0% and 50.6%, respectively. Table 2 shows the seizure frequency before and after topiramate therapy. Of all children, there was a significant difference in seizure frequency between before and after topiramate therapy ($p<0.05$). In partial-epileptic patients, six children (33.3%) achieved ≥ 50% frequency reduction, and eight children (44.4%) achieved a seizure-free state. In generalized-epileptic patients, three children with general tonic clonic seizures achieved a seizure-free state, and two achieved ≥ 50% frequency reduction. Two infantile spasms patients achieved a seizure-free state and one achieved ≥ 50% frequency reduction. A total 79.3% of children achieved more than 50% frequency reduction or seizure free.

Nine patients reported adverse effects during the titration period, stabilization period, or both (Table 3). The most common side effect was a poor appetite (10.0%) followed by irritability. No patient had an idiosyncratic response to topiramate.

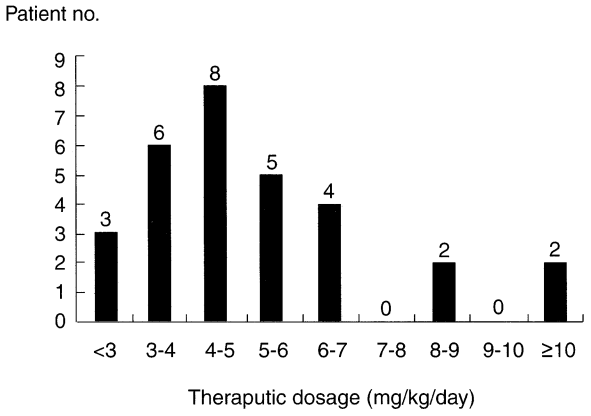

Figure 1. Therapeutic dosage (mg/kg · day) of topiramate in the 30 children.

DISCUSSION

Although being seizure free is the ultimate goal of antiepileptic drug therapy, there are still many children with intractable seizures that are hard to control using traditional drugs. Topiramate has been administered as an adjunctive antiepileptic drug to intractable epileptic patients for several years. It has been reported to be effective for infantile spasms[12,15,16], Lennox-Gastaut syndrome[12,17,18], primary generalized tonic-clonic seizures[14], and partial-onset seizures in children[13]. Previous reports showed that topiramate is a good adjunctive AED for intractable epilepsy control and has well-tolerated side effects like somnolence, anorexia, poor appetite, weight loss, etc. Our results also revealed that topiramate can decrease seizure frequency of both generalized seizures

Table 3. *Adverse effects of topiramate in 30 children*

Adverse effect	Patient No.	%
Poor appetite	3	10.0
Irritability	2	6.7
Somnolence	1	3.3
Slurred response	1	3.3
Stool incontinence	1	3.3
Hyperventilation	1	3.3

Table 2. *Seizure frequency before and after topiramate treatment for different seizure types*

Seizure type	Average seizure frequency (attacks/month)		Total patient No.	Seizure free patient No. (%)	≧50% reduction patient No. (%)
	Before TPM	After TPM			
Partial seizure	18.0	5.9	18	8 (44.4)	6 (33.3)
General tonic clonic	5.0	0.4	5*	3 (60.0)	2 (50.0)
Myoclonic	10	7	1	0 (0)	0 (0)
Absence	120	60	1	0 (0)	1 (100)
Infantile spasms	67	35	4	2 (50.0)	1 (25.0)

TPM: topiramate

*Excluded one patients discontinued topiramate due to adverse effects

and partial seizures in Taiwanese children. Thirteen patients (44.8%) achieved a seizure-free state, and ten patients (34.5%) exhibited at least a 50% reduction from their respective baseline seizure frequency.

Initially, topiramate was evaluated as an adjunctive therapy for intractable partial-onset seizures. Several double-blind, placebo-controlled adjunctive therapeutic trials were performed in adult patients[6-10]. In the study of Elterman et al.[13], they collected 86 partial-onset epileptic children (45 in the control group and 41 in the study group) aged from 2 to 16 years. Topiramate-treated patients had a greater seizure reduction rate than did placebo-control patients (33.1% compared to 10.5%). In our partial-onset epileptic children, 44.4% (8/18) achieved a seizure-free state, and a total of 85.7% (14/18) had a seizure rate reduction of ≥ 50% or were seizure free.

Topiramate is also administered adjunctively for generalized seizures including infantile spasms and Lennox-Gastaut syndrome. Biton et al.[14] enrolled 80 patients aged from 3 to 59 years (41 in the control group and 39 in the study group). The proportion of patients with a 50% or higher generalized seizure rate reduction in the study group was 46% (18/39). In our study, excluding infantile spasms, 42.3% (3/7) achieved a seizure-free state, and a total of 85.7% (6/7) had a seizure rate reduction of ≥ 50% or were seizure free.

Cross[22] reported on five children with absence epilepsy who received topiramate therapy. One patient achieved a seizure-free state, two patients had seizure reduction, and the other two patients showed no response to topiramate. There was only one child with absence epilepsy among our patients, who had a seizure reduction of ≥ 50%. Because the study group is too small, the effect of topiramate on absence epilepsy still requires additional study.

Infantile spasms and Lennox-Gastaut syndrome are challenges for antiepileptic therapy. Topiramate does not have serious side effects as does ACTH, which has been considered by many to be the treatment of choice for infantile spasms. Five infantile spasms patients (5/11, 45%) became seizure free during Glauser's study[15]. Lennox-Gastaut syndrome also showed a good response to topiramate in another of Glauser's study[12]. In our study, all infantile spasms subjects had a good response, two were spasm free, and another one had a seizure rate reduction of ≥ 50%. It was a disappointment that we did not enrolled any patient with Lennox-Gastaut syndrome.

Life-threatening idiosyncratic reactions attributed to topiramate were not found in our patients. The most prominent side effect in our study was poor appetite (10.0%). Weight loss tended to occur early in treatment and it did not appear to impact growth. Slower upward titration at the rate of 1 mg/kg · day every 1 to 2 weeks seemed to decrease the adverse effects. No renal stones were found in this study; an overall 1.5% incidence was previously reported in patients treated with topiramate[23].

One girl among our patients developed central hyperventilation after administration of topiramate. This adverse effect was possibly due to a decrease in the cerebrospinal fluid pH induced by inhibition of central carbonic anhydrase, resulting in stimulation of the central respiratory control centers[24].

Compared to other antiepileptic drugs, topiramate seems to have a favorable safety profile. Serious skin rashes like Stevens-Johnson syndrome seen when using traditional antiepileptic drugs, such as carbamazepine, phenytoin, and phenobarbital as well as new antiepileptic drug lamotrigine, have not been reported with topiramate. We found that topiramate is effective and safe for intractable epileptic children in Taiwan.

REFERENCES

1. Zupanc ML. Update on epilepsy in pediatric patients. Mayo Clin Proc 1996;71:899-916.
2. Pellock JM, Watemberg N. New antiepileptic drugs in children: present and future. Sem Pediatr Neurol 1997;4:9-18.
3. Pellock JM. Managing pediatric epilepsy syndromes with new antiepileptic drugs. Pediatrics 1999;104:1106-16.
4. Rosenfeld WE. Topiramate: a review or preclinical, pharmacokinetic, and clinical data. Clin Ther 1997;19:1294-308.
5. Rogawski MA, Porter RJ. Antiepileptic drugs: pharmacological mechanism and clinical efficacy with consideration of promising developmental stage compounds. Pharmacol Rev 1990;42:223-86.
6. Faught E, Wilder BJ, Ramsay RE, et al. Topiramate place-

bo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Neurology 1996;46:1684-90.

7. Privitera M, Fincham R, Penry J, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. Topirmate YE Study Group. Neurology 1996;46:1678-83.
8. Sharief M, Viteri C, Ben-Menachem E, et al. Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. Epilepsy Res 1992;25:217-24.
9. Tassinari CA, Michelucci R, Chauvel P, et al. Double-blind, placebo-controlled trial of topiramate (600mg daily) for the treatment of refractory partial epilepsy. Epilepsia 1996;37:763-8.
10. Ben-Menachem E, Henriksen O, Dam M, et al. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. Epilepsia 1996;37:539-43.
11. Reife R, Pledger GW, Wu SC. Topiramate as add-on therapy: pooled analysis of randomized controlled trials in adults. Epilepsia 2000;41:S66-71.
12. Glauser TA. Topiramate in the catastrophic epilepsies of childhood. J Child Neurol 2000;15:S14-21.
13. Elterman RD, Glauser TA, Wyllie E, et al. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Neurology 1999;52:1338-44.
14. Biton V, Montouris GD, Ritter F, et al. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Neurology 1999;52:1330-7.
15. Glauser TA, Clark PO, Strawsburg R. A pilot study of topiramate in the treatment of infantile spasms. Epilepsia 1998;39:1324-8.
16. Glauser TA, Clark PO, McGee K. Long-term response to topiramate in patients with West syndrome. Epilepsia 2000;41:S91-4.
17. Sachdeo RC, Glauser TA, Ritter F, et al. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Neurology 1999;52:1882-7.
18. Glauser TA, Levisohn PM, Ritter F, et al. Topiramate in Lennox-Gastaut syndrome: open-label treatment of patients completing a randomized controlled trial. Epilepsia 2000; 41:S86-90.
19. Anonymous. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Commission on classification and terminology of the international league against epilepsy. Epilepsia 1981;22: 489-501.
20. Anonymous. Proposal for classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1985;26:268-78.
21. Anonymous. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989;30:389-99.
22. Cross JH. Topiramate monotherapy for childhood absence seizures: an open label pilot study. Seizure 2002;11:406-10.
23. Bourgeois BF. New antiepileptic drugs. Arch Neurol 1998; 55:1181-3.
24. Laskey AL, Korn DE, Moorjani BI, et al. Central hyperventilation related to administration of topiramate. Pediatr Neurol 2000;22:305-8.