

Low-Dose Topiramate Is Effective in the Treatment of Infantile Spasms

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Background: Management of infantile spasms is difficult because current treatment regimens, including many anticonvulsants and hormones, are often ineffective. We conducted this study to determine the effective dose of topiramate (TPM) in Taiwanese children with infantile spasms.

Methods: Fourteen patients with infantile spasms were given TPM at an initial dose of 12.5 mg/d, and the dose was raised by 12.5 mg every 2~3 days. If the seizure frequency did not decrease during the initial 2 weeks, the dose was raised more rapidly. Titration continued for ≤ 12 weeks. Subjects were monitored by weekly visits to undergo titration.

Results: The etiology of the infantile spasms included a cryptogenic group ($n = 3$) and a symptomatic group ($n = 11$). Overall, spasms in 5 patients (38%) were completely controlled. A $\geq 50\%$ reduction in spasms was observed in 11 (85%) of 13 subjects during stabilization, while one patient quit the treatment. The mean dose of TPM during stabilization was 7.35 ± 4.9 mg/kg/d. Among these, 6 patients achieved seizure control and 3 were free of seizures at TPM doses of lower than 6 mg/kg/d.

Conclusions: Seizure control was achieved with lower doses of TPM therapy than suggested in previous studies.

(*Chang Gung Med J* 2006;29:291-6)

Key words: topiramate, infantile spasms.

Infantile spasms constitute both a distinctive seizure type and an age-specific epilepsy syndrome that have been extensively described for more than a century. Individual spasms typically are characterized by symmetric, salaam-like contractions of the trunk, with extension and elevation of the arms, and tonic extension of the legs.⁽¹⁾ Patients with infantile spasms have poor long-term prognoses, often exhibit mental retardation, and frequently undergo subsequent development of a condition called

Lennox-Gastaut syndrome. Although current therapy for infantile spasms includes anticonvulsants and hormone therapy, patients with this condition often remain resistant to both single- and multiple-drug therapies.⁽²⁾ Because of the poor prognoses of patients with infantile spasms, treatment is usually quickly and aggressively initiated after diagnosis. Most anticonvulsants are either ineffective or have serious side effects.⁽¹⁻⁴⁾ Therefore, there is a significant need for new agents that are safe and effective

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Received: Mar. 30, 2005; Accepted: Feb. 15, 2006

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in the control of infantile spasms.⁽²⁾

Topiramate (TPM) is a potent new anticonvulsant. Several pharmacological properties of TPM have been identified such as (a) enhancement of γ -aminobutyric acid (GABA) ergic influences, (b) attenuation of voltage-gated sodium currents, and (c) blockade of the α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)/kainate receptor.⁽⁵⁾ It has been used for adjunctive treatment of partial-onset seizures in children and adults,⁽⁶⁻⁹⁾ and it has also been used as monotherapy in adults with epilepsy.^(10,11) A double-blind, placebo-controlled trial using adjunctive TPM therapy in children with Lennox-Gastaut syndrome demonstrated a significant reduction in attacks and a significant improvement in seizure severity.^(12,13) In addition, TPM was shown to be an effective treatment for refractory generalized seizure types and epilepsy syndromes encountered in children.⁽¹⁴⁾

Studies using TPM therapy in patients with infantile spasms by Glauser et al. showed a significant reduction in seizure frequency, with 45% of cases becoming free of seizures.⁽²⁾ The mean dose of TPM during stabilization was 15.0 ± 5.7 mg/kg/d. Higher doses than the recommended doses were observed being used. According to the results of a Japanese study of hormone therapy, adrenocorticotrophic hormone (ACTH) therapy for infantile spasms was shown to be a successful treatment using an extremely low dose of ACTH.⁽¹⁵⁾ Therefore, there might be different effective doses of TPM for infantile spasms in Asians. We designed this study to test whether lower doses of TPM therapy was effective for the treatment of infantile spasms in Taiwanese children.

METHODS

From July 1, 2002 through June 30, 2004, 14 patients with infantile spasms were enrolled in this study. Subjects included patients with newly developed infantile spasms and those refractory to other antiepileptic drugs or hormone therapy. Infantile spasms were diagnosed by clinical manifestations and/or concomitant hypsarrhythmia on electroencephalograms.

The baseline seizure frequency was recorded for at least 2 weeks according to parental reports. Electroencephalograms and brain images were made

for all subjects before beginning TPM therapy. On completion of the baseline phase, subjects entered the titration phase. Concomitant antiepileptic drugs were not tapered off. TPM therapy was begun at 1/2 tablet (12.5 mg/d) in all subjects, and the dose was raised by 12.5 mg every 2~3 days. If the seizure frequency did not decrease in the initial 2 weeks, the dose was increased more rapidly. Titration continued for ≤ 12 weeks or until 1 of the following end points was reached: a maximal dose of 24 mg/kg/d was achieved, a maximal tolerated dose was attained, or spasms did not decrease for 7 days after an increase in the dose. Subjects were monitored by weekly visits to undergo titration. In the maintenance phase, patients were followed-up at our outpatient clinic monthly for 6 months. Spasms were reported by parents.

RESULTS

There were 9 boys and 5 girls enrolled in this study. The age at onset of spasms was from 1 to 24 (median, 7) months. The duration of spasms before the study was from 1 to 43 (median, 5) months. The age at study entry was from 4 to 53 (mean \pm SD, 21 ± 15) months. The baseline average spasm frequency was from 20 to 500 (median, 50) spasms/day. As to the etiology of infantile spasms, there were a cryptogenic group ($n = 3$) and a symptomatic group ($n = 11$). Concomitant medications averaged 1.6 ± 1.4 (range, 0~4) kinds/patient. Patients who were resistant to previous therapies averaged 2.1 ± 1.7 (range, 0~5) kinds of drugs. Previous therapies included ACTH (3), phenobarbital (5), vigabatrin (5), vitamin B6 (7), clonazepam (5), valproate (5), and lamotrigine (1). Two patients entered this study with TPM as the first anticonvulsant without previous therapy. Spasms in 3 patients were brought under control with TPM monotherapy. One patient discontinued the TPM therapy because of the bitter taste of the drug.

Ten (77%) of the subjects showed hypsarrhythmia at the beginning of the study (Table 1). In 8 of them, the hypsarrhythmia had disappeared by the stabilization stage. Overall, 5 patients (38%) became free of spasms and 4 subjects showed no hypsarrhythmia. Seven (53%) of the subjects had other types of seizures before enrollment, including complex partial seizures ($n = 2$), complex partial seizures with secondary generalization ($n = 2$), generalized

Table 1. Clinical Features of 13 Patients with Infantile Spasms

	Seizure reduction	TPM dose (mg/kg/d)	Time to achieve stabilization (day)	Etiology	Age at entry (month)	Duration of spasms before study (month)	Concomitant medications	EEG before TPM	EEG after stabilization
1*	total	2.5	7	Tuberculous meningitis	10	1	B6	hypsarrhythmia	hypsarrhythmia
2*	total	5.2	9	Cryptogenic	11	4	none	hypsarrhythmia	negative
3*	total	2.3	4	Tuberous sclerosis	11	4	none	hypsarrhythmia	focal sharp waves
4*	75%	5.2	14	Periventricular leukomalacia	34	6	VPA, CLNZ	hypsarrhythmia	focal spikes
5*	50%	2.3	70	Cryptogenic	24	5	PB	multifocal spikes	ND
6*	50%	1.1	28	Hypoxic-ischemic encephalopathy	53	43	B6	focal spikes	ND
7	total	10.8	28	Tuberous sclerosis	17	11	VGB, LTG, CLNZ, B6	hypsarrhythmia	focal spikes
8	total	11.1	35	Tuberous sclerosis	21	5	VPA, B6	hypsarrhythmia	focal sharp waves
9	75%	13.9	42	Metabolic disorder	9	1	VPA	focal spikes	ND
10	75%	7.5	21	Hypoxic-ischemic encephalopathy	19	5	PB	hypsarrhythmia	ND
11	75%	8.4	14	Tuberous sclerosis	25	1	CLNZ, B6	hypsarrhythmia	focal spikes
12	25%	17.1	49	Cryptogenic	6	2	PB	hypsarrhythmia	negative
13	25%	8.3	56	Hemimegalencephaly	4	4	PB, VGB, B6	hypsarrhythmia	cortical dysfunction

Abbreviations: TPM: topiramate; PB: phenobarbital; VPA: valproate; B6: vitamin B6; VGB: vigabatrin; CLNZ: clonazepam; LTG: lamotrigine; ND, not done.

* Six patients with infantile spasms achieved good seizure control with very low doses of TPM (< 6 mg/kg/d).

tonic-clonic seizures (n = 2), and unspecified seizures (n = 1).

Totally, a $\geq 50\%$ reduction in spasms was observed in 11 (85%) of the 13 subjects during stabilization, including 5 who were free of spasms, 4 who had $\geq 75\%$ reduction in the frequency of spasms, and 2 who had $\geq 50\%$ reduction in the frequency of spasms. The mean dose of TPM during stabilization was 7.35 ± 4.9 (range, 1.1~17.1) mg/kg/d. Among these, 6 patients (46%) achieved good seizure control with a TPM dose of < 6 mg/kg/d (Table 1). Three of them were free of seizures. They were monitored for 6 months with no seizure relapse.

The discomfort reported by the parents included poor appetite and body weight loss (n = 4), irritability (n = 3), sleep disturbance (n = 2), lethargy (n = 2), anhidrosis (n = 1), and an unstable body temperature (n = 1).

DISCUSSION

Although vigabatrin is an important new anti-convulsant for treating infantile spasms, its lack of availability in some countries (including the US), relapse rate, reported association with the development of other seizure types during therapy, and adverse effects of visual field defects imply that additional effective anticonvulsants for children with infantile spasms are needed.^(2,16,17) TPM has been reported to have the same effects in the treatment of infantile spasms (45% with TPM vs. 43% with vigabatrin) in the study of Glauser et al.⁽²⁾ Watemberg et al. also showed significant effects of TPM in the treatment of infantile spasms.⁽¹⁸⁾

High doses (up to 24 mg/kg/d, with a mean dose of 15.0 ± 5.7 mg/kg/d) and rapid titration rates were used in the study by Glauser et al.⁽²⁾ All 11 patients

with infantile spasms reported at least 1 adverse event, which was most commonly, irritability.⁽²⁾ In our study, using the modified method of Glauser et al.,⁽²⁾ we had a lower starting TPM dose and a lower titration rate to test whether there was a different maintenance dose of TPM for the treatment of infantile spasms. In our study, spasms in 38% of patients were completely controlled, and 85% of subjects experienced a $\geq 50\%$ reduction in spasm frequency. The mean dose of TPM was 7.35 ± 4.9 mg/kg/d. This is lower than those reported in studies by Glauser et al.^(2,19) Moreover, 6 patients (46%) achieved good seizure control with TPM doses of lower than 6 mg/kg/d. Seizures were completely controlled in 3 of them with TPM doses of 2.3, 2.5, and 5.2 mg/kg/d, respectively. We found that doses lower than the usual recommended dosage of TPM achieved good seizure control in patients with infantile spasms in this study. In addition, very low doses of TPM also showed remarkable effects in some cases. In our study, we did not discontinue the concomitant antiepileptic drugs. That might have been a factor affecting the results from previous studies. Nevertheless, seizures in 2 of our cases were completely controlled using low-dose TPM monotherapy, and in 1 using a combination with pyridoxine.

In the treatment of epilepsy, there have been some reports about lower doses proving to be as effective as higher doses, including with ACTH and lamotrigine for West syndrome.^(15,20) Cianchetti et al. suggested that there might be a peculiar pathogenic mechanism in some cases of West syndrome which respond to a lower dose of lamotrigine, not present for other drugs active in treating West syndrome (possibly involving inhibition of glutamate release).⁽²⁰⁾ In a Japanese study, Ito suggested that combination therapy with GABAergic drugs such as vitamin B6, valproate, benzodiazepine, tiagabine, vigabatrin, and ACTH may produce synergistic effects on seizures in patients with West syndrome.⁽¹⁵⁾ Therefore extremely low-dose ACTH therapy might achieve good seizure control in patients with infantile spasms. In our study, seizures in patients 2 and 3 were completely controlled within a short time (9 and 4 days, respectively) using low doses (5.2 and 2.3 mg/kg/d) of TPM monotherapy. The results indicate that lower doses of TPM are effective for infantile spasms in some cases. Another 4 patients with low doses of TPM were given combination therapy

with vitamin B6, phenobarbital, valproate, and clonazepam. We do not know if there is a synergistic effect with combination therapy, because we did not discontinue the concomitant anticonvulsants. Further study is necessary to determine this.

Body weight loss and the bitter taste of the drug were the main complaints by parents in this study. Because there were no sprinkle capsules available in our hospital, 1 patient discontinued the TPM therapy due to the bitter taste. The decreasing appetite in patients was tolerated by parents and the patients themselves. In a previous study using a high dose of 8.3~23.7 mg/kg/d TPM, irritability and sleep disturbance were the main reported adverse effects, and irritability in 3 patients was significant to necessitate a temporary dose reduction.⁽²⁾ In our study, the reported adverse effects were not severe enough to discontinue or reduce the dose of TPM. In general, patients maintained low doses of TPM, and few adverse events were observed in this study.

In summary, control of infantile spasms was achieved with good results using low doses of TPM therapy in this study. A decreased appetite and the bitter taste of the drug were the main complaints by parents. Generally, patients tolerated the TPM therapy well with mild side effects. We found that TPM at low doses is an effective antiepileptic drug, as monotherapy or add-on therapy, in the treatment of infantile spasms.

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低劑量 Topiramate 可以有效治療嬰兒點頭式痙攣

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背景：治療嬰兒點頭式痙攣非常困難，因為目前使用的抗抽搐藥物及賀爾蒙療法通常不是很有效。我們設計這個實驗來驗證 Topiramate 治療嬰兒點頭式痙攣的有效劑量。

方法：14 位嬰兒點頭式痙攣的病人使用 topiramate 初始劑量 12.5 mg / 天，之後每 2 到 3 天增加 12.5 mg。如果前 2 週病人抽搐頻率沒有明顯改善，則增加劑量會加快。劑量調整期為 < 12 週。病人每週追蹤。

結果：嬰兒點頭式痙攣的原因分為隱性原因組（共 3 人）和症狀原因組（共 11 人），其中總共有 5 個人（38%）痙攣完全消失，另外我們發現完成計畫的 13 個病人當中有 11 個人（85%）痙攣減少超過 50%；一人嫌藥苦而中斷治療。在穩定期的 topiramate 平均劑量為 7.35 ± 4.9 mg/kg/d。在這些人當中，有 6 個人以低劑量 topiramate 小於 6 mg/kg/d 達到痙攣控制，其中有 3 個人完全沒有痙攣。

結論：嬰兒點頭式痙攣可以用較以前建議更低劑量的 topiramate 來達成痙攣的控制。
(長庚醫誌 2006;29:291-6)

關鍵字：topiramate，嬰兒點頭式痙攣。

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受文日期：民國94年3月30日；接受刊載：民國95年2月15日

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