Original Article

Topiramate Add-on Therapy for Adult Patients with Refractory Epilepsy in Japan

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Abstract

Purpose: To evaluate the efficacy and tolerability of topiramate (TPM) as add-on therapy in Japanese adult patients with refractory epilepsy.

Methods: We performed a retrospective open-label study on 39 Japanese adult patients with refractory seizures (aged 18-64 years, average

36.4 years). Twenty-nine patients with symptomatic partial epilepsy, seven with symptomatic generalized epilepsy, two with Lennox-Gastaut syndrome, and one with severe myoclonic epilepsy in infancy were included in the study. TPM was started at a dose of 50 mg/day in 33 patients and 100 mg/day in 6 patients,

and adjusted according to individual clinical response at a slow titration of 50 mg/day or less biweekly. We compared the number of seizures in 4-week durations before and 24 weeks after starting TPM therapy.

Results: After a follow-up period of 28 weeks, 12 of 39 (31%) responded to TPM at an average dose of 100 mg/day, and four (10%) became seizure free. Thirty-one percent did not respond to TPM and 38% dropped out. Adverse events occurred in 21 patients (54%), 9 of whom discontinued TPM due to serious adverse events such as severe somnolence, depression, leg edema, excitement, and agranulocytosis. Adverse events developed even at the initial TPM dose of 50 mg/day.

Conclusion: TPM add-on therapy is effective even at low-dose in Japanese adult patients with refractory epilepsy. However, dose escalation as slow as 25 mg/day every 2 weeks is recommended to avoid adverse effects of TPM.

Introduction

Drug therapy with antiepileptic drugs (AEDs) is the mainstay of epilepsy treatment. Seizures can be controlled with AED monotherapy in many patients; however, combination therapy of more than one agent is required in more than 30% of the patients, and many of them remain refractory [1]. In addition to older AEDs that are effective to control epileptic seizures [2], the development of newer AEDs has increased the available treatment options. Topiramate (TPM), a structurally novel AED,

is a sulfamate-substituted derivative of the monosaccharide D-fructose [3]. TPM is considered to produce its antiepileptic effects primarily through (a) blockade of voltage-dependent sodium channels in the neuronal membrane; (b) blockade of voltage-dependent calcium channels in the neuronal membrane; (c) negative modulating effect at kainite α -amino - 3 - hydroxyl - 5 - methyl - 4-isoxazolepropionate (AMPA) glutamate receptors; (d) enhancement of γ -aminobutyric acid (GABA) activity at GABA_A receptors; and (e) inhibition of carbonic anhydrase isoenzymes, although the precise mechanism of action has not been fully elucidated [4]. TPM has been proven to be effective as an adjunctive AED for partial epilepsy [5], generalized epilepsy [6], and Lennox-Gastaut syndrome [7]. Its efficacy and safety have been shown by several clinical studies in adult patients, not only in the United States and European countries [8, 9], but also in Asian countries including Taiwan [10], Republic of China [11], and Korea [12]. We conducted this investigation to assess the clinical effectiveness and adverse reactions of TPM in Japanese adult patients with refractory epilepsy.

Methods

Patients

We retrospectively reviewed the medical records and collected clinical data of the patients treated at the epilepsy clinic of Utano National Hospital between December 2007 and October 2009, including age, sex, seizure

type, epilepsy classification, and AEDs used. Thirty-nine patients who fulfilled the following inclusion criteria were enrolled: (1) a well-established diagnosis of epilepsy as defined by the classification of epilepsies and epileptic syndrome (ILAE, 1989) [13]; (2) initiation of TPM as add-on therapy; (3) adult; (4) a history of intractable seizures in spite of treatment using two or more kinds of AEDs in adequate doses. The epilepsies were classified accord-

ing to the proposed Classification of Epilepsies and Epileptic syndromes (ILAE, 1989) [13]. Seizure types were classified according to the International Classification of Epileptic Seizures (ILAE, 1981) [14] based on the observation of clinical symptoms by family members and co-medical personnel. The demographic characteristics of patients are shown in Table 1. Five patients (13%) were taking five AEDs before adding TPM, 3 (8%)

Table 1. Patient demography and disease description (n=39).

Demography/clinical data	
Gender, male/female, n	22 /17
Mean age, years (range)	36.4 (18-64)
Number of AEDs at start of observation, n (%)	
1 AED	2 (5)
2 AEDs	15 (38)
3 AEDs	14 (36)
4 AEDs	3 (8)
5 AEDs	5 (13)
Seizure frequency before treatment with TPM, n (%)	
Daily	16 (41)
Weekly	13 (33)
Monthly	10 (26)
Epilepsies and epileptic syndrome, n	
TLE	14
FLE	9
OLE	1
Cryptogenic	5
GE	9
SMEI	1
Seizure classification, n	
SPS	19
CPS	25
2 nd GS	9
Generalized seizures	8

AED=antiepileptic drug; TLE=temporal lobe epilepsy; FLE=frontal lobe epilepsy; OLE=occipital lobe epilepsy; GE=generalized epilepsy; SMEI=severe myoclonic epilepsy in infancy; SPS=simple partial seizure; CPS=complex partial seizure; 2nd GS=secondarily generalized seizure.

were taking four AEDs, 14 (36%) were taking three AEDs, 15 (38%) were taking two AEDs, and only 2 (5%) were on monotherapy. Regarding seizure frequency, 16 patients (41%) had daily, 13 (33%) had weekly, and 10 (26%) had monthly seizures. According to the epilepsy classification system, 29 patients had symptomatic partial epilepsy (SPE), comprising 14 with temporal lobe epilepsy (TLE), 9 with frontal lobe epilepsy (FLE), 1 with occipital lobe epilepsy (OLE) and 5 cryptogenic patients. Nine patients had generalized epilepsy (GE), comprising 7 with symptomatic generalized epilepsy and 2 with Lennox-Gastaut syndrome (LGS). One patient had undetermined epilepsy syndrome of severe myoclonic epilepsy in infancy (SMEI). For a total of 61 documented seizures, 19 were classified as simple partial seizures (SPS), 25 as complex partial seizures (CPS), 9 as secondarily generalized seizures (2nd GS), and 8 as generalized seizures. Generalized seizures could not be further classified based on the information obtained from witnessed persons.

Treatment

Target dose and dose escalation of TPM were based upon the physician's decision. Previous studies revealed that weekly dose escalation of 50 mg/day was associated with a lower incidence of premature drug withdrawal than that of 100-200 mg/day, without any delay in efficacy [15, 16]. Therefore in this study, the starting dose of TPM was 50 mg/day in 33 patients and 100 mg/day in six patients, and then increased gradually at a bi-

weekly increment of 50 mg/day or less.

Evaluation and Assessments

The effectiveness and adverse events of TPM were evaluated by clinical information obtained from the patients and attendants during the study period. We compared the number of seizures in 4-week durations before and 24 weeks after starting TPM therapy. The efficiency of TPM was evaluated as the proportion of responders, that is, patients who became seizure-free or achieved more than 50% reduction in seizure frequency.

Results

Responses of epilepsies and seizures

After a follow-up period of 28 weeks, 12 of 39 (31%) patients responded to TPM and four of them (10%) became seizure free. Twelve patients (31%) did not respond to TPM. Fifteen patients (38%) dropped out: 9 patients stopped TPM due to adverse events, 4 quitted TPM by their own will, and 2 were lost to follow-up. Table 2 shows the responsive cases. The mean TPM dose at seizure reduction was 100 mg/day in these patients. Of 29 patients with SPE, 4 became seizure-free and 4 had more than 50% seizure reduction, resulting in a responder rate of 28%. Of 9 patients with GE, 3 (33%) had more than 50% seizure reduction. The only one patient with SMEI investigated had more than 50% reduction of seizures. The responder rates by seizure type were 32% for SPS, 28% for CPS, 44% for 2nd GS, and 25% for generalized seizures.

Tolerability and safety

A total of 24 adverse events were documented in 21 patients (54%) and somnolence was the most common event ($n = 11$). Details of the adverse events are provided in Table 3a. TPM treatment was tolerated by 12 patients, 4 of whom had dose reduction. However, 9 patients (23%) discontinued TPM due to serious adverse events: severe somnolence in 4, de-

pression in 2, leg edema in 1, excitement in 1, and agranulocytosis in 1 [17]. Twenty adverse events (83%) were reported during 8 weeks after starting TPM. However, four adverse events occurred later than 8 weeks: appetite loss in 9 weeks, irritation in 10 weeks, depression in 16 weeks, and excitement in 22 weeks. Adverse events developed even at the initial TPM dosage of 50 mg/day (Table 3b).

Table 2. Responsive cases.

Case	Age/sex	Epilepsies	Responded seizure types	Seizure reduction (%)	Response dose (mg/day)	Concomitant medications
1	32/M	SPE	SPS, CPS	100	100	CBZ
2	51/M	SPE	CPS	100	150	VPA, CBZ, NZP
3	18/M	SPE	SPS, CPS, 2 nd GS	100	50	CBZ, AZA, PHT
4	36/M	SPE	SPS, CPS, 2 nd GS	100	200	PB, CBZ, VPA
5	39/F	SPE	CPS	>50%	200	VPA, CBZ, CLB, PHT, DZP
6	40/F	GE	GS	>50%	50	VPA, AZA
7	32/M	SMEI	GS	>50%	100	VPA, CZP, ZNS, CLB, BrK
8	18/F	GE	GS	>50%	50	VPA, AZA
9	26/M	SPE	SPS, CPS	>50%	100	CBZ, CLB
10	25/M	SPE	CPS	>50%	50	PHT, CLB, PB, AZA, GBP
11	32/F	GE	CPS, GS	>50%	100	VPA, ZNS, CLB
12	36/F	SPE	SPS, GTC	>50%	50	CBZ, VPA, NZP
Mean					100	

SPE= symptomatic partial epilepsy; GE=generalized epilepsy; SMEI=severe myoclonic epilepsy in infancy; SPS=simple partial seizure; CPS=complex partial seizure; 2nd GS=secondarily generalized seizure, GS=generalized seizure; CBZ=carbamazepine; VPA=valproate; NZP=nitrazepam; AZA=acetazolamide; PHT=phenytoin; CLB=clobazam; BrK=potassium bromide.

Discussion

The efficacy and safety of TPM have already been confirmed by many previous controlled clinical trials not only in Western countries but also in Asian countries. TPM was introduced to Japan in 2007 and has been used as an add-on drug for the treatment of refractory partial epilepsies. In a phase III clinical trial of adult patients with refractory

epilepsies in Japan, which set a target dose of 400 mg/day, the responder rate was approximately 33% [18]. Previous studies of TPM add-on therapy in patients with refractory epilepsies reported responder rates of 48-50% in Asian countries [10, 19, 20], and 40-50% in Europe and United States [4-6]. In the present study, the responder rate was 31% and 10% of the patients achieved freedom from seizure by

Table 3a. Numbers of adverse events.

Adverse events	Number of events
Somnolence	11
Irritate	4
Depression	2
Appetite loss	2
Nausea	1
Headache	1
Excitement	1
Leg edema	1
Agranulocytosis	1

Table 3b. Onset time of adverse events and TPM doses.

Adverse events	Onset time of adverse events (weeks)											Mean TPM dose (mg/day)
	1	2	3	4	5	6	8	9	10	16	22	
Somnolence	4		2	3		1	1					82
Irritate			1	1		1			1			63
Depression						1				1		75
Appetite loss							1	1				50
Nausea				1								100
Headache		1										50
Excitement											1	100
Leg edema					1							100
Agranulocytosis				1								200

adding TPM to 1 to 5 concomitant AEDs. The responder rate in this study was equivalent to the previous clinical trial in Japan [18] in spite of lower TPM doses of less than 200 mg/day, which was slightly lower than that used in other countries. Several studies have demonstrated the clinical efficacy of low-dose TPM. Guberman et al. [21] showed the therapeutic effectiveness with TPM at 100 mg/day. The Korean Topiramate Study Group reported no difference in responder rate between patients treated with less than 200 mg/day and with 200-300 mg/day [12]. Therefore, even with lower doses of TPM, a clinically relevant seizure reduction can be achieved.

When the epilepsies were classified according to the international classification of epilepsies and epileptic syndrome, the responder rates were 28% in SPE, 33% in GE, and 100% in SMEI. The responder rates by seizure type were 22 % in SPS, 28% in CPS, 44% in 2nd GS, and 25% in generalized seizures. Similar to previous reports [8, 12], therapeutic effects were seen not only in patients with partial epilepsies and partial seizures, but also in those with generalized epilepsies, generalized seizures, and SMEI.

The frequency of adverse events was 54% in our study, which was lower than that of a previous study in Japan (81%) that used an initial dose of 100 mg/day and rapid dose escalation (weekly increment of 100 mg/day) [18, 22]. Marked decrease in incidence of adverse events was reported by slower dose titration schedules [15, 16, 19]. Therefore we adopted an initial dose below 100 mg/day and

slower dose titration of biweekly increment of 50 mg/day or less. Even with this regimen, frequent occurrence of adverse events could not be prevented. Therefore, even slower dose escalation of 25 mg/day every 2 weeks is recommended to avoid side effects of TPM. Except agranulocytosis and leg edema, the adverse events reported during this study were known to occur with TPM therapy [23]. Most of these events were seen within 8 weeks, which was similar to previous report [19]. However, four patients developed adverse events in 20 or 30 weeks. Later occurrence of adverse events should be notified because Cho et al. [20] reported a patient who committed suicide 2 years and 11 months after starting TPM add-on therapy.

In summary, this study characterized the efficiency and adverse events of TPM add-on therapy in adults with refractory epilepsy in Japan. For better therapeutic efficacy and less adverse events, an initial TPM dose of less than 100 mg/day and dose escalation slower than biweekly increment of 50 mg/day are recommended.

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