

## The efficacy of topiramate in status epilepticus, experience from Thailand

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### Abstract

**Background:** Oral topiramate is a broad-spectrum antiepileptic drug. There is limited documented data on its use in refractory convulsive and non-convulsive status epilepticus. **Methods:** A retrospective study of the clinical characteristics and responses of patients diagnosed as status epilepticus treated with topiramate at the Srinagarind Hospital, Khon Kaen University from 2001-2010. **Results:** There were 8 patients included in this study, 6 patients were convulsive status epilepticus and 2 patients were non-convulsive status epilepticus. The most common cause was stroke seen in 4 patients. Oral topiramate successfully controlled status epilepticus in 7 out of 8 patients with no serious adverse events. Of these 7 patients, status epilepticus was controlled after initial loading and re-loading of oral topiramate in 3 and 4 patients, respectively. In two patients with hepatitis, oral topiramate was successful after failure with benzodiazepine. The initial loading dose of topiramate in most cases was 400 mg with a maintenance dose of 100 mg/day.

**Conclusion:** Oral topiramate has the potential to treat both convulsive and non-convulsive status epilepticus after failing the first antiepileptic drug. Further study with larger number of patients is needed to confirm this.

### INTRODUCTION

Status epilepticus (SE) is a life-threatening emergency condition that requires prompt and proper management with intravenous (IV) antiepileptic drugs (AEDs). The most common first-line AEDs therapy is IV benzodiazepine, either lorazepam or diazepam. If seizures persist, the second-line such as phenytoin, fosphenytoin or sodium valproate are often given. In case of refractory SE, phenobarbital, propofol, or sodium thiopental are recommended medications.<sup>1-3</sup>

Topiramate (TPM), a sulfamate-substituted monosaccharide, is an oral, broad-spectrum AEDs approved as adjunctive and monotherapy in the treatment of epilepsy. There are multiple mode of action involving blockade of voltage-dependent sodium channels, potentiation of GABAergic transmission and inhibition of excitatory pathways through an action at AMPA receptor sites. Carbonic anhydrase inhibiting properties have also been demonstrated.<sup>4</sup> The pharmacokinetics of TPM are characterised by linear pharmacokinetics over the dose range 100-800mg, which, in monotherapy, is predominantly through renal excretion (renal clearance 10-20 mL/min) and can be used in patients with hepatic impairment.<sup>5</sup> It has minimal protein binding and a long half-life

(19-25 hours). TPM is well absorbed from the gastrointestinal tract. Oral availability is 81-95% and is not affected by food intake. A peak plasma level is usually attained in 2-3 hours. TPM has little effect on the plasma concentrations of other AEDs except phenytoin. TPM metabolism is increased when administered with carbamazepine or phenytoin.<sup>4,6-7</sup> Adverse effects of TPM include ataxia, decreased concentration, confusion, dizziness, and fatigue.<sup>1,8</sup>

The appropriate dosage of TPM ranges from 50 mg and up to 1,000 mg as monotherapy or add-on therapy.<sup>4,6,9-12</sup> Privitera *et al*<sup>13</sup> showed that an initial target dose of TPM 100 mg/day is at least as effective as therapeutic doses of carbamazepine and valproate and some studies have suggested that most patients are likely to benefit from receiving 400 mg day or less. Higher dose TPM treatment is associated with side effects, especially CNS-related.<sup>4</sup>

TPM has been reported to be effective in both refractory and non-convulsive SE which are unresponsive to standard AEDs.<sup>2</sup> The use of TPM in SE was first reported by Reuber in 2002.<sup>14</sup> Since then, case series have been published in both adult and children. In adult patients, Bensalem and Fakhoury<sup>15</sup> reported the effectiveness of TPM

in treating SE in 3 patients, Towne *et al.*<sup>16</sup> in 6 cases, Soler *et al.*<sup>17</sup> in 3 cases, Stojanova *et al.*<sup>18</sup> in 4 of 7 cases. Synowiec *et al.*<sup>19</sup> reported success in 14 out of 35 cases, and needed no further IV anesthetic agents or additional AEDs in 3 days. In the pediatric population, Kahriman *et al.*<sup>20</sup> reported that success in 3 children, Blumkin *et al.*<sup>21</sup> in 2 cases, and Perry *et al.*<sup>22</sup> in 3 cases. Akyildiz and Kumandas<sup>23</sup> reported TPM use in 14 patients. Of those, 9 patients had full response, 3 patients had partial response, and 2 patients did not respond. In Asia, Xiong *et al.*<sup>24</sup> reported the first case of TPM use in a child with SE.

Despite these, clinical data of oral TPM treatment in SE is still limited, particularly among the Asians. In Thailand, TPM has been commonly used in SE with hepatitis and refractory SE in the recent years, partly because IV phenobarbital has not been available in Thailand since 2009. We report here the clinical features and outcomes of 8 SE patients treated with oral TPM at Khon Kaen University Hospital (Srinagarind hospital), Thailand.

## METHODS

This is a retrospective study based on the review of the 2001 to 2010 hospital database. Srinagarind Hospital is a tertiary care university hospital located in the Northeastern part of Thailand. There were 8 SE patients who were treated with oral TPM over the study period. Clinical features, electroencephalography (EEG) findings and treatment outcomes of the patient were reviewed.

SE was defined as ongoing seizures or repetitive seizure activity without a recovery of consciousness between seizures for more than 30 min.<sup>2</sup> Diagnosis of non-convulsive SE was based on EEG. Brain imaging (CT or MRI), laboratory work-up and CSF analysis were performed as clinically indicated.

Responses to TPM were determined by clinical assessment because of EEG service was not available during weekends and out-of-working hours. The definition of seizure control was as follows: "Complete control" was when there was no clinical evidence of seizure, or an increase of alertness and responsiveness after loading or re-loading of TPM without any seizure recurrence; "Partial control" was when there was no clinical evidence of seizure after loading or re-loading TPM but had recurrence during maintenance phase; "No response" was when there was ongoing seizures despite loading and re-loading with TPM.

## RESULTS

There were 8 SE patients who received oral TPM during the study period. Six patients had convulsive SE and 2 patients had non-convulsive SE. The patients consisted of 7 females and one male. The mean age was 54 years, range 18 to 76 years. The etiology of SE was stroke (4 patients), viral meningoencephalitis (2 patients), and one patient each for SLE and malignant catatonia. The initial loading dose of TPM was 400 mg in 6 patients, 300 mg and 600 mg in one patient each. The maintenance dose of 100 mg/day. Oral TPM successfully controlled the SE in 7 out of 8 patients with no serious adverse events. Of the 7 patients, SE was successfully controlled after initial loading in 3 patients, and with re-loading in 4 patients. Both patients with hepatitis (cases 3, 6) who were given TPM after failure of diazepam responded to TPM. There were no adverse events attributable to the TPM in any of the patients. Four patients died due to hospital acquired pneumonia or pulmonary embolism. The summary of patients' clinical data is shown in Table 1.

### Case 1

This 73 year old right-handed woman was admitted due to a 2-week history of recurrent abnormal behavior, and generalized tonic-clonic seizures (GTC). One day prior to admission, she had repetitive attacks of talking to herself with automatism. On physical examination, she was unconscious and had no motor weakness. A CT-scan brain showed an old cerebral infarction in the right frontal lobe and left internal capsule. The electroencephalogram (EEG) revealed epileptic discharges in the right fronto-parieto-temporal areas and secondary generalization. Diagnosis of complex partial seizure with secondary GTC SE was made. She was treated with IV diazepam followed by, IV fosphenytoin and IV sodium valproate, but the seizures persisted. Oral loading of TPM 400 mg was given. The seizures stopped but SE relapsed 8 hours later. Re-loading with 400 mg and 600 mg oral TPM was given and the SE was completely controlled. The patient regained consciousness and fully recovered. She was given the maintenance dose of TPM 100 mg/day.

### Case 2

This was a 43 years old right-handed woman with past history of systemic lupus erythematosus (SLE) and systemic sclerosis. She was admitted with a history of acute fever, severe headache and altered consciousness. On neurological

**Table 1. A summary of the 8 patients with status epilepticus treated by oral topiramate.**

Sex/ Age	Underlying disease	Etiology	Seizure type	EEG	Previous AED	Loading dose of TPM (mg)	Initial response	Re-loading dose of TPM (mg)	Maintenance dose of TPM (mg/day)	Final result	Outcome (cause of death)
1 F/73	DM,HT CKD,CAD	Stroke (CI)	CSE	Primary epileptic foci at right fronto-parieto- temporal areas and secondarily generalized to both cerebral hemispheres	DZP FosPHT VPA	400	Stop, and recurred at 8 hr	1,000	100	Completely controlled	Complete recovery, no handicap
2 F/43	Systemic sclerosis, SLE, HT, RF	Acute viral meningo- encephalitis	CSE	Primary epileptic foci at right fronto-parietal areas and secondarily generalized to both cerebral hemispheres.	DZP VPA	400	Stop, and recurred at 3 hr	400	100	Completely controlled	Complete recovery, same handicap
3 F/42	SLE	SLE	CSE	Primary epileptic foci at right fronto-parietal areas and secondarily generalized to both cerebral hemispheres.	DZP	300	Completely controlled	No	100	Completely controlled	Death, non seizure related (HAP)
4 F/66	No	Malignant catatonia	CSE	Epileptic foci at left temporal area, and secondarily to both cerebral hemispheres	DZP PHT VPA	400	Completely controlled	No	100	Completely controlled	Death, non seizure related (PE)
5 F/76	DM, HT, CKD	Stroke (CI)	NCSE	Diffuse and generalized spike and wave	DZP VPA	600	Completely controlled	No	100	Completely controlled	Death, non seizure related (HAP)
6 F/74	Autoimmune hemolytic anemia	Stroke (ICH) HIE	NCSE	Primary epileptic foci at right temporo - parietal areas and secondarily generalized to both cerebral hemispheres	DZP	400	Stop, and recurred at 22 hr	400	100	Completely controlled	Death, non seizure related (HAP)
7 F/18	No	Viral meningo- encephalitis	CSE	no	DZP VPA	400	Stop, and recurred at 48 hr	400	CBZ was a maintenance AED	Partially controlled	Complete recovery, no handicap
8 M/35	Thyroid storm, AF	Stroke (CI)	CSE	no	DZP VPA	400	Stop, and, recurred at 8 hr	800	100	Completely controlled	Complete recovery, same handicap

M: Male, F: Female;

CI: Cerebral infarction, ICH: Intracerebral hemorrhage, HIE: Hypoxic ischemic encephalopathy

DM: Diabetes mellitus, HT: Hypertension, CKD: Chronic kidney disease, CAD: Coronary artery disease, SLE: Systemic lupus erythematosus, RF: Renal failure, AF: Atrial fibrillation

CSE: Convulsive status epilepticus, NCSE: Non-convulsive status epilepticus;

AED: Antiepileptic drug, DZP: Diazepam, VPA: Sodium valproate, PHT: Phenytoin, FosPHT: Fosphenytoin, PB: Phenobarbital, TPM: Topiramate;

HAP: Hospital acquired pneumonia, PE: Pulmonary embolism

examination she was in stupor with neck stiffness. Her CT-scan brain was normal. The cerebrospinal fluid examination showed white blood cells of 27 cells/mm<sup>3</sup> (neutrophil 59%), protein of 116 mg/dL, and sugar of 73 mg/dL (blood sugar 107 mg/dL). CSF Gram's stain and culture were negative. Acute viral meningoencephalitis was diagnosed and the patient developed SE during the admission. EEG showed right fronto-parietal discharges with secondary generalization. She was initially treated with IV diazepam and then IV sodium valproate loading, but SE was not controlled. She was then loaded with oral TPM at 400 mg, and the seizures stopped. However, after 3 hours, SE recurred. She was then re-loaded with oral TPM 400 mg, and the seizures were controlled. She was treated with oral TPM 100 mg/day for maintenance.

#### Case 3

This was a 42-year-old, right-handed woman with history of SLE. She was admitted with pneumonia. Ten days after admission, she developed generalized tonic-clonic (GTC) SE. On neurological examination she was in stupor and had generalized weakness. The CT brain scan was normal. The EEG showed epileptiform discharges at the right fronto-parietal area with secondary generalization. The cerebrospinal fluid showed white blood cells of 10 cells/mm<sup>3</sup> (neutrophil 40%) with protein of 79 mg/dL, and sugar of 44 mg/dL (blood sugar 130 mg/dL). CSF Gram's stain and culture were negative. Cerebral lupus was diagnosed. She was initially treated with IV diazepam but SE was not controlled. Because she had an abnormal liver function test (ALT 258 U/L, AST 723 U/L), oral TPM 300 mg loading was prescribed and SE was controlled. Oral TPM 100 mg/day was used as maintenance therapy. However the patient died from hospital acquired pneumonia and septic shock.

#### Case 4

A 66-year-old woman presented with abnormal behavior where she said repeatedly the same sentence for two months. Neurological examination showed generalized muscle rigidity and a waxy posture. Malignant catatonia was diagnosed. After admission, GTC SE occurred. EEG showed epileptic foci at the left temporal area, and secondary generalization. The seizure did not respond to IV diazepam, IV phenytoin and IV sodium valproate treatment. Oral TPM 400 mg loading with 100 mg/day for a maintenance dose successfully controlled the SE. This patient

subsequently died from pulmonary embolism.

#### Case 5

A 76-year-old woman with type 2 diabetes mellitus, hypertension, and chronic kidney disease was admitted due to alteration of consciousness. Her weight was 100 kg and serum creatinine was 2.5 mg/dL. She was diagnosed to have non-convulsive SE, based on EEG showing generalized spike-and-wave complexes. She did not respond to IV diazepam and IV sodium valproate. Oral TPM 600 mg loading and 100 mg/day maintenance dose successfully controlled the SE. She later died from hospital acquired pneumonia, septic shock and liver failure.

#### Case 6

A 74-year-old woman with autoimmune hemolytic anemia was admitted with a 2 day history of confusion, and left hemiparesis. CT brain scan showed intracerebral hemorrhage at the right temporo-parietal area. EEG also showed epileptic foci at right temporo-parietal areas with secondary generalization. Nine days after admission, the patient had cardiac arrest. She did not regain consciousness after successful cardio-pulmonary resuscitation. The EEG showed periodic sharp and slow waves and paroxysmal frequent spikes with paroxysmal 3.5Hz spike-and-wave complexes, with diagnosis of non convulsive SE. She did not improve with IV benzodiazepine. Because of an abnormal liver function test (ALT 219 U/L, AST 220 U/L), oral TPM 400 mg loading was given. Her SE shown in EEG improved after an additional 400 mg TPM. This patient died, however, from hospital acquired pneumonia and septic shock.

#### Case 7

An 18-year-old woman was admitted with viral meningoencephalitis. She had a history of phenytoin allergy. Two days after admission, she developed GTC SE, which did not respond to IV diazepam and IV sodium valproate. Double doses of TPM 400 mg resulted in only partial control of the SE, which was later controlled by IV phenobarbital.

#### Case 8

A 35-year-old man was admitted with left middle cerebral artery infarction, aspiration pneumonia, thyroid storm and atrial fibrillation. Two days after admission, he developed GTC SE. SE was partially controlled with IV diazepam and IV

**Table 2. Comparison of the present study with the previous studies in adult population**

	Current study 2012	Bensalem and Fakhoury 2003 <sup>15</sup>	Towne <i>et al.</i> 2003 <sup>16</sup>	Soler <i>et al.</i> 2009 <sup>17</sup>	Stojanova <i>et al.</i> 2011 <sup>18</sup>	Synowiec <i>et al.</i> 2012 <sup>19</sup>
No. of patient	8	3	6	3	11	35
Age	18-76 year	31-75 year	39-72 year	24-59 year	18-80 year	19-88 year
Seizure type	6 CSE, 2 NCSE	2 CSE, 1 CPS	2 PSGTC, 2 CPS, 1 Partial NCSE, 1 FM	2 PSGTC, 1 NCSE	5 CSE, 4 CPS, 2 NCSE	No data
SE etiology	1.Stroke	1.Subacute encephalopathy	1.Encephalitis	1.Cryptogenic	1.Encephalitis	1. Infection (23%)
(First three)	2.Encephalitis	2.Hepatic encephalopathy	2.Stroke	2.Encephalitis	2.Post-cerebral trauma	2.Low AEDs level (14%)
	3.Uremic encephalopathy	3.Post anoxic seizure	3.Remote meningioma	3.Hypoxic ischemic encephalopathy	3.Stroke	3.Intracranial hemorrhage (14%)
Dose	LD 400 mg MD 100 mg/day	LD 500 mg bid x 2 days MD 200 mg bid	Max 300-1,600 mg/day	100-400 mg bid	Max 50-800 mg/day	LD 200-400 mg Total dose 100-800 mg/day
Response	7 complete controlled 1 partial controlled	3 response in day 2	4 response in 24 hr 1 response in 48 hr 1 response in 10 day	2 response in 48 hr 1 response in 72 hr	2 response in 12-72 hr 2 possible response in 72-96 hr 7 non-response	14 response in 3 day
Adverse effect	no	no	no	no	1 severe nephrolithiasis	no

CSE: Convulsive status epilepticus, NCSE: Nonconvulsive status epilepticus, CPS: Complex partial seizure, PSGTC: Partial seizure with secondary generalization, FM: Focal motor  
LD: Loading dose (LD), MD: Maintenance dose

sodium valproate. SE was controlled with triple doses of 400 mg oral TPM loading and a 100 mg/day maintenance dose.

## DISCUSSION

Oral TPM successfully treated SE in 7 out of 8 patients in this series. Six patients were convulsive SE and two patients were non convulsive SE. A loading dose of 400 mg with maintenance dose of 100 mg/day was typically used. SE was completely controlled by oral TPM loading in three patients (Case 3, 4, 5), while four SE patients were successfully controlled with additional oral TPM loading (Case 1, 2, 6, 8). There were no adverse events from the TPM.

After the routine treatment with 10 mg IV benzodiazepine, oral TPM was used as the next line of therapy in one patient, the second line in one, the third line in 4, and fourth line in 2 patients. Two patients who had TPM as the initial AEDs because of hepatitis (Case 3, 6) responded to oral TPM. Most of the SE patients had unstable vital signs; a relative contraindication for IV thiopental loading. In this series, all of the deaths resulted from non-seizure related complications, such as hospital acquired pneumonia and pulmonary embolism, despite the control of seizures in most patients.

Oral TPM was reported to be used in SE with different regimens and times to seizure control varied.<sup>14-24</sup> (Table 2) Stojanova *et al.*<sup>18</sup> reported that 7 out of 11 SE patients were not responsive to oral TPM treatment. In that study, there were higher numbers of complex partial seizure SE and the maximum dosage of TPM was 50 mg which is lower than other studies.<sup>14-17,19</sup> The disadvantage of TPM treatment in SE is a lack of parenteral formulation.<sup>3</sup> Therefore, it may require 12-48 hours of oral TPM administration for SE to be terminated.

The limitation of this series was that not all patients had EEG performed. The diagnosis of SE, however, was made based on the clinical criteria.<sup>25</sup> Even though oral TPM is highly effective in this case series, further clinical studies are needed.

In conclusion, oral TPM has the potential as initial or adjunctive therapy of SE. It should be considered in the management of refractory SE or when other AEDs are contraindicated, as in significant hepatitis.

## DISCLOSURE

Conflict of Interest: None

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