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Effectiveness of Topiramate in Medically Complicated Patients with Status Epilepticus or Acute Refractory Seizures

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Background and Purpose: The conventional therapeutic regimen for status epilepticus (SE) may require artificial ventilation and hemodynamic support, and is associated with significant complications and increased mortality. We investigated the safety and effectiveness of topiramate (TPM) in patients with refractory SE, who had medical complications such as systemic infection, renal dysfunction, hepatic dysfunction, and bone marrow suppression.

Methods: We analyzed the clinical features and therapeutic outcome in 16 patients with GCSE, NCSE or recurrent GTC in whom TPM was administered for its control.

Results: The majority of our patients had GCSE (n=6) or NCSE (n=7). The common co-morbid diseases at the onset of seizures were hematological disorders (pancytopenia 8, anemia 2, anemia with thrombocytopenia 2) and sepsis (n=8). Twelve patients were under the renal and/or hepatic dysfunction. Within a few days, 13 patients could experience their seizure control (the mean duration, 3.7± 2.6 days), but the seizures of the other subjects did not be terminated in spite of all efforts. No patients experienced a worsening of their CBC or blood chemistry profiles with the TPM treatment.

Conclusions: We could confirm that TPM was not only safe but very effective for the control of recurrent epileptic seizures or SE in patients with serious medical co-morbidities. TPM may be considered as another treatment option when conventional protocols are ineffective. **(2011;1:52-56)**

Key words: Recurrent seizures; Status epilepticus; Topiramate

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Introduction

Generalized convulsive status epilepticus (GCSE) and non-convulsive status epilepticus (NCSE) are important neurological conditions potentially associated with significant morbidity and mortality.[1] Even with the best current practice, the mortality of patients with refractory GCSE is up to 50%. Therefore, there is an urgent need for new treatment options that can treat these seizures safely and more effectively than the current standard drugs.[2]

The most common treatment protocols for status epilepticus include an intravenous benzodiazepine, either lorazepam (LZP) or diazepam, as the initial antiepileptic drug (AED) therapy, followed by phenytoin (DPH) or fosphenytoin. Phenobarbital (PB) is added if the seizures continue.[3] A pharmacologically induced coma, using the barbiturates, propofol or midazolam, is also a frequently used therapy for refractory status epilepticus (RSE),[2,4,5] which is defined as the persistence of discrete seizures without return to baseline, despite treatment with benzodiazepines and at least two adequate AEDs.[6,7] However, it requires artificial ventilation and hemodynamic support, and is associated with significant complications and increased mortality.[2,4]

Topiramate (TPM) is an AED with demonstrated efficacy for a broad spectrum of seizure types[8]; it has multiple activities at receptors and ion channels that may be more effective than conventional anticonvulsants in treating RSE.[7,9]

We report our experience with the use of TPM for the treatment of benzodiazepine-refractory status epilepticus (SE) or recurrent seizures in 16 patients who are under severe medical complications such as systemic infection, renal dysfunction, hepatic dysfunction, and pancytopenia from bone marrow suppression.

Methods

We retrospectively identified patients with GCSE or NCSE who were treated with TPM at our hospital between July 15, 2006 and August 10, 2008. The medical records were reviewed for information regarding patient characteristics, associated medical conditions, type of SE (GCSE or NCSE), duration, abnormal laboratory findings, treatment history prior to administration of TPM, and outcome.

Hepatic dysfunction was defined as an AST and ALT >200 mg/dL and renal dysfunction was defined as a serum creatinine >2.0 mg/dL and a creatinine clearance <0.6. Anemia was defined as a hemoglobin <12.0 g/dL, thrombocytopenia as a thrombocyte count <150,000/mm^3 and pancytopenia as a leukocyte <4,000/mm^3 with anemia and thrombocytopenia. Administration of AEDs, other than TPM, followed our hospital's protocol: LZP (4 mg) was injected intravenously and DPH (15 mg/kg) or VPR (20 mg/kg) were infused intravenously for 30 minutes. TPM tablets were crushed to powder and mixed with water before administration. The mixture was allowed to sit for several minutes to avoid clumping and then administered via syringe into a nasogastric tube. The loading dose was individualized by patient; 6-12 mg/kg/day, up to 1,000 mg/day. The resolution of recurrent GTC and GCSE was determined by cessation of clinical seizures, and confirmed by follow-up electroencephalopgrahy (EEG). For NCSE, The resolution of seizures was determined by continuous EEG monitoring.

Results

From the database on SE patients, 16 patients were identified for inclusion in this study. The individual cases are summarized in Table 1. Eight patients were male. The mean age was 50.4±18.3 (14-79 years). No patient had a history of seizures or was receiving TPM or other AEDs prior to admission. The most common previous, co-morbid disease at the onset of seizures was sepsis (n=8). The laboratory studies showed that 12 patients had hematological problems (pancytopenia 8, anemia alone 2, and anemia with thrombocytopenia 2). Seven patients had renal dysfunction, three patients had hepatic dysfunction only and another four patients had both renal and hepatic dysfunction. The majority of patients had experienced GCSE (n=6) or NCSE (n=7). Three patients had repetitive GTC. The mean TPM treatment dose was 637.5±244.6 mg (300-1,000 mg). Within a few days, 13 patients could experience their seizure control (the mean duration, 3.7±2.6 days; range 1-8 days), but the seizures of the other 3 subjects did not be terminated in spite of all efforts. None of the patients had a worsening of their CBC or blood chemistry profiles with the TPM treatment. For seven patients, the TPM was administrated after the failure of the loading of high doses of DPH or VPR. The administration of TPM was within 2 hours after the infusion of DPH or VPR. The seizures stopped in six patients after treatment with TPM. The overall outcome was described as follows: patient death (n=11), improved (n=4), transferred to another hospital (n=1). The causes of 11 deaths were sepsis (n=7), fulminant hepatitis, SAH, hypoxic brain damage, and herpes encephalitis.

We now represent two illustrative cases using TPM for controlling recurrent seizures from a variety of medical derangement.

Case 1 (patient 4) with GCSE

A 48-year-old woman with no history of seizures was admitted to the hospital in poor health. The patient was diagnosed with paroxysmal nocturnal hemoglobinuria (PNH) 20 years prior to admission and had been treated as an outpatient with oral steroids. RBC transfusions were performed once a month. The routine blood tests on admission revealed pancytopenia (hemoglobin 4.4 g/dL, hematocrit 13.3%, WBC 730/mm^3, and a platelet count of 52,000/mm^3) and acute renal failure (BUN 126.5 mg/dL and creatinine 9.23 mg/dL). Continuous renal replacement therapy (CRRT) was performed in the intensive care unit. On the third hospital day, GCSE developed. Treatment was started with a LZP injection followed by DPH infusion. However, the GCSE continued. A loading dose of TPM (800 mg) was administrated via a nasogastric tube. By the next day, the continuous seizures were under control and the patient was responsive to verbal stimulation. However, intermittent brief seizures occurred several times under a maintenance dose of TPM (300 mg bid) during the subsequent two days. After three days of TPM administration the seizures stopped. The follow-up EEG showed no epileptiform discharges. The diffusion-weighted MRI revealed multifocal high signal intensity involving the occipital lobes, the right basal ganglia and the subcortical white matter of the prefrontal gyri on the diffusion and T2-weighted images. The identified lesions showed increased values on the ADC map, suggesting vasogenic edema or a posterior reversible encephalopathy (PRES). The EEG showed multifocal sharp waves and intermittent generalized slow waves. The TPM was maintained at a dose of 200 mg bid, and there was no further seizure activity. However, aspiration pneumonia and sepsis developed, and the patient died on the 15th

Table 1. Clinical characteristics of 16 patients with refractory recurrent seizures treated with topiramate

Pt#	Sex	Age	Sz type	Medical condition	Hematologic abnormalities	Abnormal lab finding in	Emergency Therapy	Combined medication for sz control	TPM loading (mg)	Outcome of Seizures	Sz duration (days)	Overall Outcome
1	M	61	GCSE	CRF, Hypoxic damage	Anemia	Kidney	LZP →TPM		800	Continued until expire	>13	E (hypoxic damage)
2	M	48	GCSE	PNH		Kidney	LZP →DPH loading →TPM		400	Stopped	1	Improved
3	F	51	GCSE	Multiple myeloma, pneumonia, Sepsis	Pancytopenia	Kidney, Liver	LZP →DPH loading →TPM	CLB 20 mg, VPR 1200 mg	800	Stopped	3	E (sepsis)
4	F	48	GCSE	PNH, ARF	Pancytopenia	Kidney,	LZP →DPH loading →TPM	CLB 40 mg	800	Stopped	3	E (sepsis)
5	M	79	GCSE	Pneumonia, Sepsis, ARF		Liver	LZP →DPH loading →TPM	CLB 10 mg	400	Stopped	7	Improved
6	M	31	GCSE	ALL, Pneumonia, Sepsis	Pancytopenia	Kidney	LZP →VPR loading →TPM	CLB 20 mg	500	Continued until death	>12	E (sepsis)
7	M	67	NCSE	Sepsis, Nephrotic syndrome			LZP →TPM		800	Stopped	1	E (sepsis)
8	F	32	NCSE	Lymphoma, Herpes encephalitis	Pancytopenia	Kidney	LZP →TPM		1000	Stopped	8	E (HSE)
9	F	56	NCSE	Multiple myeloma, Sepsis	Pancytopenia	Liver	LZP →TPM		600	Stopped	5	E (sepsis)
10	F	45	NCSE	Lung abscess			LZP →TPM		300	Stopped	1	Improved
11	M	67	NCSE	Viral encephalitis	Anemia	Liver	LZP →TPM		800	Stopped	7	Improved
12	F	14	NCSE	AML, GVHD, Sepsis, Hyponatremia	Pancytopenia	Kidney	LZP →DPH loading →TPM		300	Stopped	5	E (sepsis)
13	M	75	NCSE	Pneumonia, Sepsis, ARF	Anemia, TP	Kidney	LZP →DPH loading →VPR loading →TPM		600	Continued until transfer	>3	F/U loss
14	F	66	Repetitive GTC	Fulminant hepatitis, CRF, Old stroke	Pancytopenia	Kidney, Liver	LZP →TPM	GPT 300 mg	800	Stopped	1	E (liver failure)
15	M	36	Repetitive GTC	ALL, Pneumonia, Sepsis	Pancytopenia	Kidney, Liver	LZP →TPM	GPT 1800 mg	300	Stopped	1	E (sepsis)
16	F	31	Repetitive GTC	SLE, TTP, SAH	Anemia, TP	Kidney, Liver	LZP →TPM	OCZP 600 mg	1000	Stopped	3	E (SAH)

Sz, seizure; TP, thrombocytopenia; LZP, lorazepam; DPH, phenytoin; VPR, valproate; CLB, clobazam; GPT, gabapentin; OCZP, oxcarbazepine; GTC, generalized tonic clonic; E, expired; HSE, herpes encephalitis; SAH, subarachnoid hemorrhage.

hospital day.

Case 2 (patient 9) with NCSE

A 56-year-old woman was admitted to the hospital with impaired mental status. The patient had a history of multiple myeloma (stage IIIa) diagnosed three years prior to the admission; she received chemotherapy several times, but the disease was refractory to chemotherapy. VAD chemotherapy using vincristine, doxorubicin and dexamethasone was started. However, generalized seizures developed during the third cycle of chemotherapy, and the patient became unresponsive with her eyes deviated to the right side. The routine blood tests revealed pancytopenia (hemoglobin 5.2 g/L, hematocrit 14.4%, WBC 4,570/mm^3, and a platelet count of 15,000/mm^3), and septic shock developed. Continuous EEG monitoring showed bilateral rhythmic slow waves dominating the frontal area. NCSE was diagnosed and TPM (300 mg bid) was administrated. The epileptiform discharges disappeared after five days, the patient recovered and was responsive. However, the blood culture revealed *Staphylococcus epidermidis*, and she died on the 49th hospital day from septic shock.

Discussion

We described 16 patients with GCSE, NCSE or recurrent GTC in whom TPM was administered alone or together with other AEDs. Most patients with overt, convulsive status epilepticus respond to the first or second AED. However, when the patient fails to respond to this standard protocol during the initial treatment, the patient is considered "refractory" and requires additional, more aggressive treatment.[3] RSE is a life-threatening condition that carries a high mortality risk. Aggressive, early intervention permitting avoidance of a pharmacological coma can reduce the overall morbidity and mortality.[4] Current recommendations for the treatment of refractory status epilepticus include midazolam (MDZ), pentobarbital and propofol.[10] However, respiratory depression and/or hypotension may result from this treatment, which may necessitate endotracheal intubation and/or vasopressor support .[10,11] Oral AEDs such as TPM or LEV, however, have much to offer if they can pre-empt these more aggressive managements.[12]

TPM has at least five independent actions at the cellular level[13]: inhibition of kainate-evoked currents, enhancement of γ-aminobutyric acid (GABA)-evoked currents, blockage of voltage-activated sodium channels, blockage of voltage-activated calcium channels, and inhibition of carbonic anhydrase isoenzymes. The multiple mechanisms of action confer broad-spectrum efficacy against different seizure types and make TPM an attractive choice in the treatment of both partial and generalized SE.[14] Since TPM has pleiotropic effects on neuronal excitability, a favorable pharmacokinetic profile and appears to have few side effects in the setting of RSE, it is a reasonable therapeutic option in patients with SE.[3] TPM is also considered appropriate for treatment of patients with of hepatic or renal disease. It does not significantly increase the risk of hepatotoxicity and renal disease is not a contraindication to the use of TPM.[15]

There are some reports on the use of TPM in SE patients. Reuber *et al.*[16] reported a patient with drug-resistant complex partial SE who responded to TPM. Towne and colleagues described six adult patients with a variety of types of SE who were unresponsive to conventional treatment, including two who also failed to respond to treatment with pentobarbital.[7] A suspension of TPM administered by a nasogastric tube was effective in aborting the RSE in all cases. Remarkably, no adverse events were observed and all six patients who survived and were discharged from the hospital. Bensalem et al. also described the use of TPM via a nasogastric tube in three patients with RSE (two with generalized seizures and one with partial seizures).[14] TPM appeared to be very effective in stopping the RSE; in two of the patients that were resistant to either pentobarbital or propofol, and no adverse effects were noted. Perry *et al.*[17] reported the effectiveness of TPM loading for RSE in children. Patients who had SE after therapeutic doses of at least two antiepileptic medications were given TPM, 10 mg/kg/d for consecutive days, followed by maintenance doses of 5 mg/kg/d. In each case, the SE was stopped within 21 hours of the initial dose of TPM.

In our study, the seizures of subjects were terminated both clinically and electrographically in 13 out of 16 patients. The timing of improvement in our patients was within 1-8 days of starting the administration of TPM. These findings are consistent with the pharmacokinetic properties of TPM and previous reports. In six cases, given TPM after loading with DPH or VPR failed, TPM successfully stopped the seizures, even in medically complicated patients.

Although seizures were stopped clinically and electrographically in the majority of our patients, the overall outcome was not very favorable in our study. This is likely due to the serious underlying medical conditions of the patients enrolled. All of the nine patients who with pancytopenia died even though the seizures were controlled. The high mortality rate of the patients studied reflects the large number

of leukemia and lymphoma patients treated in our hospital. The majority of the patients studied had serious and often life threatening hematological problems such as pancytopenia or thrombocytopenia.

One of the limitations of this study was the heterogeneity of our patients. They had a variety of medical comorbidities, including systemic infection, hepatic or renal dysfunction and hematologic/oncologic disorders. However, our results convincingly support that TPM is safe and effective in a special group of seriously ill patients.

Conclusion

We could find that TPM was not only safe but very effective for the control of recurrent epileptic seizures or SE in patients with serious medical co-morbidities. TPM may be considered as another treatment option when conventional protocols fail. A large prospective, randomized, controlled study is warranted to investigate the efficacy and safety of TPM for the treatment of SE.

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