Epilepsy Research (2012) **98**, 232—237

journal homepage: www.elsevier.com/locate/epilepsyres

The efficacy of topiramate in adult refractory status epilepticus: Experience of a Tertiary Care Center

Andrea S. Synowiec[a], **Kristin A. Yandora**[a], **Vamsi Yenugadhati**[a], **James P. Valeriano**[a,b], **Carol J. Schramke**[a,b], **Kevin M. Kelly**[a,b,c,*]

[a] *Department of Neurology, Allegheny General Hospital, Pittsburgh, PA, USA*
[b] *Department of Neurology, Drexel University College of Medicine, Philadelphia, PA, USA*
[c] *Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA, USA*

Received 16 June 2011; received in revised form 19 September 2011; accepted 26 September 2011
Available online 15 October 2011

KEYWORDS
Refractory status epilepticus;
Seizures;
Topiramate;
Antiepileptic drugs;
$GABA_A$ receptor;
Glutamate receptors

Summary Refractory status epilepticus (RSE) occurs in patients with SE when they fail to respond to traditional medical therapy. Because there are very few case reports of topiramate (TPM) treatment of RSE in adult patients, we examined our experience with TPM with regard to its safety and efficacy in seizure termination in RSE in an adult patient population. We report a retrospective review of 35 adult patients with RSE who were treated with TPM in addition to other antiepileptic drugs (AEDs) between 2003 and 2010. After failure of initial treatments of benzodiazepines and weight-based intravenous loading doses of standard AEDs, TPM tablets were crushed and administered via nasogastric tube. Data were collected on age, gender, history of epilepsy, etiology of RSE, daily dose of TPM, co-therapeutic agents, treatment response, and disposition. Following initiation of TPM use and discontinuation of continuous intravenous anesthetics with no additional AEDs administered, cumulative cessation of RSE in patients was 4/35 (11%) at one day, 10/35 (29%) at two days, and 14/35 (40%) at three days. However, when including all patients and comparing the two patient groups in which RSE was or was not terminated within three days of initiating TPM as the last or not last AED given, there was no significant difference. Time to TPM response was not associated with the type of seizures, etiology of SE, or whether there was a history of epilepsy. There were no documented side effects or complications of therapy with TPM. This study provides support for the use of TPM as an adjunctive agent in the treatment of RSE.

Introduction

Status epilepticus (SE) is a life-threatening medical emergency characterized by either ongoing or intermittent seizure activity without complete recovery between seizures for a duration of at least 30 min and is associated

* Corresponding author at: Allegheny General Hospital, 940 ST, 320 East North Avenue, Pittsburgh, PA 15212, USA.
Tel.: +1 412 359 3467; fax: +1 412 359 6127.
E-mail address: kelly@wpahs.org (K.M. Kelly).

0920-1211/$ — see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2011.09.017

with significant morbidity and mortality. When patients fail to respond to traditional therapies, they progress to refractory SE (RSE), which occurs in 10—40% of patients with SE (Lowenstein, 2006). In some patients, RSE may continue for weeks or even months despite treatment, a situation termed malignant RSE (Abend and Dlugos, 2008). Various definitions of RSE have been utilized, including those based on time frame, persistence of seizure activity, or failure of a certain number of antiepileptic drugs (AEDs) (Kahriman et al., 2003; Perry et al., 2006). Despite the lack of a formalized definition, RSE is often associated with lengthy and complicated patient hospitalizations, higher overall functional disabilities, and poor outcomes (Lowenstein, 2006).

There is currently no consensus on a standardized treatment protocol for RSE. Most clinicians initially follow treatment protocols for SE, which typically outline intravenous benzodiazepine therapy followed by administration of phenytoin or fosphenytoin. When seizures continue, phenobarbital may be given (Lowenstein and Alldredge, 1998). When these measures fail to control seizures, continuous intravenous anesthetics are often initiated with the use of propofol, midazolam, or pentobarbital. When the patient is unable to wean from these coma-inducing medications without seizure recurrence, the clinician will typically choose additional AEDs for use based upon availability, safety concerns, and potential efficacy.

A small number of reports has described the use of topiramate (TPM) in RSE, most of which recount experience with pediatric patients. Blumkin et al. (2005) found that TPM was efficacious and able to be titrated rapidly, leading to cessation of refractory partial SE in two young children. Kahriman et al. (2003) reported cessation of RSE within 24 h of adjunctive maintenance therapy with TPM at doses of 5—6 mg/kg/day in three children. Perry et al. (2006) demonstrated cessation of seizures within 21 h in three pediatric patients after loading with high-dose TPM. Finally, Akyildiz and Kumandas (2011) reported 14 pediatric patients who were treated with TPM with varying degrees of success.

Three short reports exist in the literature regarding the use of TPM for treatment of RSE in the adult population. Towne et al. (2003) showed termination of RSE in six adult patients using TPM, whereas Bensalem and Fakhoury (2003) demonstrated efficacy in treating three adult patients. Soler et al. (2009) had success using TPM in another series of three adults with RSE.

Our institution has had increased use of TPM as adjunctive treatment of RSE in adults over the last decade. Because of the relatively few adult patients in whom TPM's efficacy has been reported, we sought to describe our experience with TPM in the treatment of adult RSE and determine whether our experience supported the clinical impression that TPM was safe and efficacious with regard to termination of seizures and patient disposition.

Methods

The Institutional Review Board of Allegheny General Hospital approved this study and granted waiver of informed consent and HIPAA authorization. A retrospective analysis was performed via chart review of adult patients identified as experiencing RSE between 2003 and 2010. Patient hospital charts from this eight-year period were screened for RSE using diagnostic billing codes assigned at the time of hospital discharge, including grand mal status, generalized nonconvulsive epilepsy with intractable epilepsy, epilepsia partialis continua, or epilepsy unspecified, and were reviewed to identify patients with RSE who were treated with TPM. RSE was defined as persistence of seizure activity despite appropriate medical therapy for at least 24 h, or the inability to wean from continuous IV anesthetics without seizure recurrence. Patients were monitored with either continuous EEG or intermittent EEG, the latter at variable intervals no longer than 24 h. Patients in nonconvulsive RSE demonstrated ictal discharge patterns consistent with primary electrographic criteria for nonconvulsive seizures (Jirsch and Hirsch, 2007). Cessation of RSE was defined as no clinical or electrographic seizures for at least 24 h immediately following discontinuation of the IV anesthetic.

Forty-six patients were diagnosed with RSE and treated with TPM during the eight-year period. We excluded seven patients because TPM was being used at the time of SE onset. Two patients were excluded for incomplete outcomes data due to transfer from our facility during acute care for insurance reasons. Two patients were excluded due to early withdrawal of care precipitated by medical complications. The remaining 35 patients were assessed for this study. These patients were initially unresponsive to a standard treatment protocol of benzodiazepines and weight-based intravenous loading doses of standard AEDs. These treatments were usually followed by continuous infusions of benzodiazepines or propofol, along with additional administration of AEDs. Following failure of these treatments, TPM tablets were crushed and administered via nasogastric tube. Data were collected on age, gender, history of epilepsy, etiology of RSE, daily dose of TPM, cotherapeutic agents, treatment response, and disposition. Because TPM was not the last non-anesthetic AED given to all patients prior to termination of RSE, we compared those patients who did and did not receive TPM as the last AED administered. This comparison was performed to determine whether there were differences between these patient groups that might help to elucidate which patients were more likely to respond to TPM. Using *t*-tests or Fisher's exact tests as appropriate, we tested for between group differences in age, gender, and history of epilepsy. In all 35 patients who had termination of RSE, we tested whether there was a correlation between the duration of RSE prior to TPM's use and the time to termination of RSE after TPM was administered. Mean data are presented with the standard deviation. Effects with a p-value <0.05 were considered significant.

Results

RSE was terminated in all 35 patients studied. Etiologies of RSE in our patient group included infection (23%), low AED level (14%), intracranial hemorrhage (14%), metabolic abnormality (9%), drug or alcohol overdose or withdrawal (9%), trauma (6%), stroke (3%), anoxia/hypoxia (3%), and unknown (20%). TPM was the last non-anesthetic AED used in the majority (28/35, 80%) of cases. In those seven patients who received additional medications, these medications were added one to ten days following initiation of TPM (mean 5.3 days, s.d. = 3.2). Most patients received TPM doses of 100 mg every 4 or 6 h; five of these patients were given an initial single loading dose prior to the scheduled dosing (Table 1). In virtually all cases, serum TPM levels were not obtained.

For all 35 patients, the mean age was 57.7 (s.d. = 21.7) years. For the 28 patients receiving TPM as the last AED administered, the mean age was 58.5 (s.d. = 22.5) years and for those seven patients who received additional agents, the mean age was 54.7 (s.d. = 19.7) years; these numbers were