Seizure 2002; **11**: 57–59
doi:10.1053/seiz.2001.0560, available online at http://www.idealibrary.com on IDEAL®

CASE REPORT

Non-convulsive status epilepticus induced by tiagabine in a patient with pseudoseizure

YU ZHU & BRADLEY V. VAUGHN

Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514, USA

Correspondence to: Bradley V. Vaughn, CB7025, Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7025, USA. *E-mail*: vaughnb@glial.med.unc.edu

Tiagabine, a novel GABA reuptake inhibitor, has been reported to induce non-convulsive status epilepticus (NCSE) in patients with epilepsy. We report a 27 year old female with history of pseudoseizure documented by video-EEG monitoring who presented confusion while on 56 mg per day of tiagabine. Electroencephalography showed generalized sharp and slow wave discharges, consistent with NCSE. The NCSE was terminated by lorazepam and did not recur after tiagabine was discontinued. This case report suggests that tiagabine may induce NCSE in patients without epilepsy.

Key words: tiagabine; non-convulsive status epilepticus; pseudoseizure; GABA; benzodiazepine.

INTRODUCTION

Tiagabine (TGB) has been approved as an add-on antiepileptic drug therapy for partial seizures. This medication appears to block neuronal and glial reuptake of gamma-aminobutyric acid (GABA) and thus increase synaptic GABA concentration[1]. In a pre-marketing clinical trial, 0.8% (3/494) of patients treated with TGB developed status epilepticus compared with 0.7% (2/275) of placebo-treated patients[2]. In 1996, Schapel and Chadwick reported three cases of non-convulsive status epileptics (NCSE) in association with 48–60 mg per day use of TGB[3]. Subsequent reports[4–6] demonstrate that NCSE occurred in patients with partial onset and primary generalized seizures when given TGB at a dose between 30 and 60 mg per day. In the previously reported cases of NCSE, all patients had epilepsy documented by EEG. Here we report a case of TGB-induced NCSE in a patient with documented pseudoseizure.

CASE REPORT

NT is a 27 years old African-American female. At age 13, the patient developed typical events that consisted of body thrashing, kicking, stiffening followed by unresponsiveness for a few minutes and a complete recovery. These events occurred more frequently during stressful time periods and interfered with her ability to work. The patient had normal routine EEGs. She was then video-EEG-monitored in 1992 and 1995 at university affiliated EEG monitoring centers. On both occasions, her typical events were captured on video and none of these events had correlating EEG changes. The patient saw multiple physicians and was given trials of phenytoin, carbamazepine, valproic acid, gabapentin, topiramate, and lamotrigine. She was subsequently prescribed tiagabine and titrated to a total dose of 56 mg per day in the 3 months prior to admission. After three weeks on the current dose, the patient presented a 2 day history of intermittent confusion. Physical examination at the time of admission showed

Published online 20 August 2001.

1059–1311/02/010057 + 03 $35.00/0

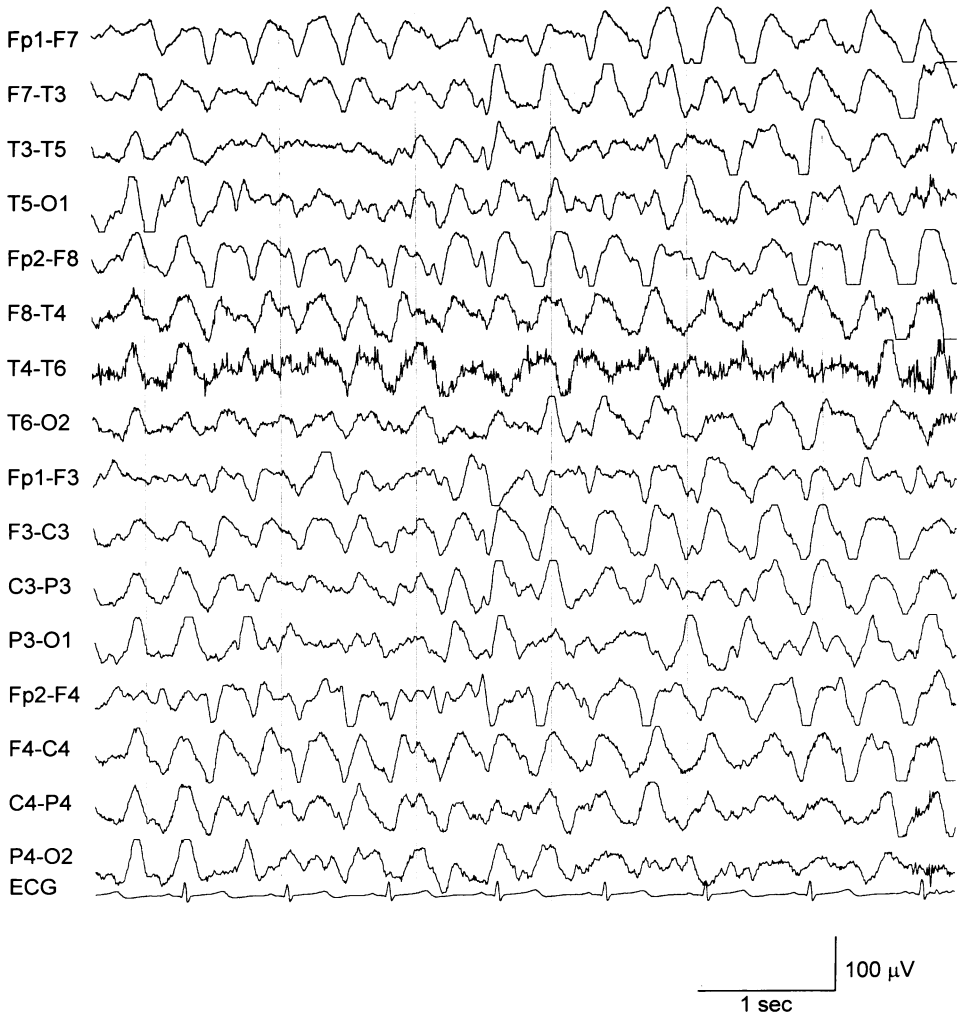

Fig. 1: EEG recordings during non-convulsive status epilepticus.

normal vital signs. The patient was lethargic but arousable, disoriented and slow in speech. Otherwise, neurological examination was normal. Head CT at the time of admission was unremarkable. Routine laboratory studies (including renal and liver function tests) showed no abnormality. Video-EEG monitoring revealed generalized sharp and slow wave discharges (Fig. 1), consistent with an ictal pattern of NCSE. The patient was given 2 mg of lorazepam intravenously, which was then repeated once within 10 minutes. Her mental status significantly improved and her EEG returned to normal. TGB was discontinued and the patient was observed over the next 24 hours. During the observation, she remained alert and oriented. She then had two episodes of her typical events including asynchronous body arching, thrashing, and avoidance behavior that intermittently waxed and waned over several minutes. These events had no corresponding epileptiform changes on the EEG. Her neurological examination was normal following each of these events, and prolactin levels did not change when measured 20 and 60 minutes following one event.

DISCUSSION

TGB has been known to induce NCSE in patients with epilepsy[3–6]. In our patient, the patient had previously documented pseudoseizures and developed NCSE while on TGB. To our knowledge, this is the first report that TGB induced NCSE in a patient without epilepsy. The patient demonstrated, on three separate video-EEG monitoring sessions at three different university affiliated centers, episodes which were concluded to be non-epileptic. The behavioral features that lack a discrete end to the events and the absence of both EEG changes and a rise in prolactin levels suggested that the patient's typical events were non-epileptic. However, it should be acknowledged that the patient might have true epilepsy that was not revealed

by scalp EEG recordings. The NCSE induced by TGB may be a manifestation of her underlying epilepsy. In this sense, TGB may function as a diagnostic agent in this patient.

The mechanism for TGB to induce NCSE is not clear. GABA is a major inhibitory neurotransmitter in the CNS. After its release from presynaptic vesicles, GABA is taken back by GABA transporters to presynaptic nerve terminals and glial cells. Four types of GABA transporters in humans have been identified, i.e. GAT-1, GAT-2, GAT-3, and BGT-1. TGB appears to inhibit GAT-1 specifically with an IC_{50} around 70 nM[7]. Inhibition of GABA reuptake by TGB increases the synaptic concentration of GABA, which in turn activates both $GABA_A$ and $GABA_B$ receptors. Activation of presynaptic $GABA_B$ receptors causes presynaptic inhibition that in turn decreases further GABA release, i.e. an autoregulatory mechanism. It has been postulated that TGB-induced NCSE may be due to an inhibition of GABA release by over-activation of presynaptic $GABA_B$ receptors[4]. Over-activation of presynaptic $GABA_B$ receptors by baclofen, a $GABA_B$ receptor agonist, has been reported to induce NCSE[8]. However, TGB-induced and baclofen-induced NCSE are not analogous. In the presence of baclofen, synaptic GABA concentration is not increased and postsynaptic $GABA_A$ receptors are not highly activated. In contrast, in the presence of TGB, synaptic GABA concentration is elevated and postsynaptic $GABA_A$ receptors are highly occupied. Therefore, it would be difficult to explain how NCSE is developed in the presence of accumulated synaptic GABA.

Pre-clinical studies have shown that TGB has a weak affinity ($IC_{50} = 15\,000$ nM) for benzodiazepine receptors[9]. In a subset of patients, TGB at high doses may non-specifically bind to and block benzodiazepine receptors. If this is the case, the situation may be similar to seizures induced by flumazenil, an antagonist of benzodiazepine receptors.

TGB may induce NCSE in patients with or without epilepsy via the same mechanisms. Patients with epilepsy may be more prone to TGB-induced NCSE than those without epilepsy. However, the incidence of TGB-induced NCSE in the non-epileptic population is unknown. Like other AEDs, the use of TGB has been extended to the non-epileptic patient population, e.g. treating mood disorders[10], headache, and spasticity. One report has shown that TGB at 30 mg per day induced generalized tonic–clonic seizure in a patient with acute mania but no previous history of epilepsy[10]. Therefore, it is important for physicians to be aware that TGB may induce seizure in patients without epilepsy.

REFERENCES

1. Schachter, S. C. Tiagabine. *Epilepsia* 1999; **40** (Suppl. 5): S17–S22.
2. Shinnar, S., Berg, A., Hauser, W. A., Hesdorffer, D., Treiman, D., Leppik, I., Sillanpää, M. and Sommerville, K. Evaluation of the incidence of status epilepticus in association with tiagabine therapy. *Epilepsia* 1997; **38** (Suppl. 3): S65.
3. Schapel, G. and Chadwick, D. Tiagabine and non-convulsive status epilepticus. *Seizure* 1996; **5**: 153–156.
4. Echardt, K. M. and Steinhoff, B. J. Nonconvulsive status epilepticus in two patients receiving tiagabine treatment. *Epilepsia* 1998; **39**: 671–674.
5. Ettinger, A. B., Bernal, O. G., Andriola, M. R., Bagchi, S., Flores, P., Just, C., Pitocco, C., Rooney, T., Tuominen, J. and Devinsky, O. Two cases of nonconvulsive status epilepticus in association with tiagabine therapy. *Epilepsia* 1999; **40**: 1159–1162.
6. Trinka, E., Moroder, T., Nagler, M., Staffen, W., Löscher, W. and Ladurner, G. Clinical and EEG findings in complex partial status epilepticus with tiagabine. *Seizure* 1999; **8**: 41–44.
7. Borden, L. A. GABA transporter heterogeneity: pharmacology and cellular localization. *Neurochemistry International* 1996; **29**: 335–356.
8. Solomon, G. E. and Labar, D. Hypothesis that tiagabine-induced NCSE is associated with GABAergic hyperfunction, with $GABA_B$ receptors playing a critical role, is supported by a case of generalized NCSE induced by baclofen (letter). *Epilepsia* 1998; **39**: 1383.
9. Suzdak, P. D. and Jansen, J. A. A review of the preclinical pharmacology of tiagabine: a potent and selective anticonvulsant GABA uptake inhibitor. *Epilepsia* 1995; **36**: 612–626.
10. Grunze, H., Erfurth, A., Marcuse, A., Amann, B., Normann, C. and Walden, J. Tiagabine appears not to be efficacious in the treatment of acute mania. *Journal of Clinical Psychiatry* 1999; **60**: 759–762.