Tiagabine-induced non-convulsive status epilepticus in a patient without history of epilepsy

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ABSTRACT

Cases of non-convulsive status epilepticus (NCSE) induced by tiagabine (TGB) were occasionally reported. Almost all had a prior history of epilepsy. We describe here, the clinical and EEG findings in a patient, without history of seizures, who after the start of TGB developed NCSE. A 53-year-old man with history of paranoid schizophrenia, presented with "alteration of his mental state." Three weeks early, TGB was added to his psychiatric regimen. On the second day of admission, he became unresponsive with a blank stare. Concomitant EEG showed abundant sharp and slow wave complexes. The episode lasted for 4 hours and was aborted by the intravenous administration of lorazepam. The TGB was discontinued without recurrence of subsequent seizure activity. This case supports the contention that TGB can induce NCSE in subjects not previously known to have seizures.

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There are case reports of non-convulsive status epilepticus (NCSE) associated with tiagabine (TGB) treatment, predominantly in patients suffering from generalized or focal epilepsy.[1-5] However, a cause effect relation was contested in epidemiological studies that failed to prove an increase in the incidence of status epilepticus in patients receiving TGB for complex partial or secondarily generalized seizures.[6,7] We discuss here, a schizophrenic patient with EEG proven NCSE after the initiation of TGB therapy by his psychiatrist. He had no prior history of seizures. Physicians should be aware of this rare but potentially serious complication of TGB therapy.

Case Report. A 53-year-old man was brought to the Emergency Department (ED) with "alteration of mental state." He reportedly experienced a single generalized tonic-clonic seizure and episodic unresponsiveness with a blank stare in the few days prior to admission. His medical history was significant for paranoid schizophrenia, hypertension, type-2 diabetes mellitus, hyperlipidemia, and remote alcohol abuse. His medications included TGB 8 mg twice daily (started approximately 3 weeks earlier for mood control), clozapine 700 mg/day, olanzapine 20 mg/day, glyburide 2 mg/day, lisinopril 20 mg/day, and gemfibrozil 1200 mg/day. On examination in the ED, he was alert, and oriented. He was able to name objects and followed commands. The neurological examination was otherwise, unremarkable. His vital signs were stable. Complete blood count, electrolytes, and liver function tests were in the normal range except for a blood glucose of 186 mg/dL. Urine drug screen was negative. Head CT with contrast showed no abnormalities. He was admitted to the video EEG monitoring unit and his medications were continued unchanged. On the second night of hospitalization, he failed to respond to commands with total speech arrest. He was staring vacantly into space. The concomitant EEG showed abundant repetitive sharp waves, maximal bifrontally, intermixed with rhythmic slow waves; consistent with the diagnosis of NCSE (**Figure 1**). The episode lasted for 4 hours, aborted only after intravenous administration of lorazepam. He immediately became more responsive with prompt resolution of the sharp waves in the EEG (**Figure 2**). The TGB and clozapine were discontinued. Clozapine had to be reinstituted the next day upon insistence of the psychiatrist. Eight months later, he has not experienced any recurrent seizures and the EEG was completely normal. A head MRI revealed only mild cerebral atrophy.

Discussion. Many studies support the contention that TGB can exacerbate absence and myoclonic seizures in animal models,[8,9] leading to the general avoidance of this medication

in primary generalized epilepsy in clinical practice. The controversy concerns the link between TGB, and the induction of NCSE in patients treated for refractory complex partial seizures.[2-4] Such case reports were contested in epidemiological studies that concluded that TGB does not increase the risk of status epilepticus in patients with partial seizures.[6,7] Some of the case reports lack definitive evidence that the patient was indeed in status; a concomitant EEG is not available for all cases. Furthermore, the discrepancy may also stem from the lack of consensus regarding the EEG features that would differentiate NCSE from a drug induced toxic encephalopathy.[10] Shinnar et al,[6] classified some of the reported NCSE cases as representing only "drug intolerance".

We believe that our patient had NCSE rather than a non-epileptic toxic encephalopathy. His behavior during the event, the EEG pattern, and the prompt response to lorazepam are supportive of this contention.[10] He had no history of epilepsy, and the episode of NCSE had a temporal association to the institution of TGB for his psychiatric disorder. On admission, he was taking a daily dose of 16 mg, lower than observed in published case reports in patients with past seizures. The patient was also receiving clozapine, but it is unlikely that it was the main culprit as its dose had been stable for years, and most importantly there was no recurrence of NCSE or seizures despite continuation of the drug later. Also, clozapine is known to induce seizures of the generalized tonic clonic and myoclonic type only.[11] To our knowledge, there are no reports linking it to status epilepticus including the non convulsive type. However, clozapine is highly protein bound (97%) and can lead to an increased free fraction of TGB. Another of his medications, olanzapine was occasionally reported to cause seizures. However, this is much less common than clozapine. There is only one report associating olanzapine with convulsive status epilepticus,[12] and no reports linking it to NCSE. Tiagabine is metabolized by cytochrome P450 enzyme CYP3A4.[13] He was also taking gemfibrozil, which inhibits this enzyme. It is possible that concomitant treatment with gemfibrozil resulted in elevated serum TGB level, precipitating NCSE.

We think, TGB was the "main offender" in this case. The atypical antipsychotic drugs and gemfibrozil might have played a "facilitative" effect by lowering the seizure threshold and increasing the total and unbound serum TGB levels. The mechanism by which TGB may induce NCSE is unclear. Proposed explanations include activation of GABA B receptors or paradoxical neuronal depolarization through a GABA A receptor mediated mechanism.[14] Non convulsive epilepsy is associated with GABA hyperfunction.[9] Walton et al,[15] describe an abnormal hyporeactive state in normal non-epileptic rats after TGB administration, accompanied by high amplitude, frontally dominant, rhythmic 3-5 Hz spike wave activity on EEG. The similarities between this rat model and our patient are unmistakable.

We conclude that TGB can induce NCSE in patients with or without prior history of seizures. The occurrence of this complication with a low dose of TGB warrants caution especially when it is co-administered with drugs that lower seizure threshold, have inhibitory effects on the P45O enzyme system or high protein binding. Physicians should be aware of this rare but potential complication, when their patients on TGB develop alteration of mental state, even if they do not give a history of seizures. Timely recognition of this entity and institution of appropriate treatment would prevent unnecessary morbidity.

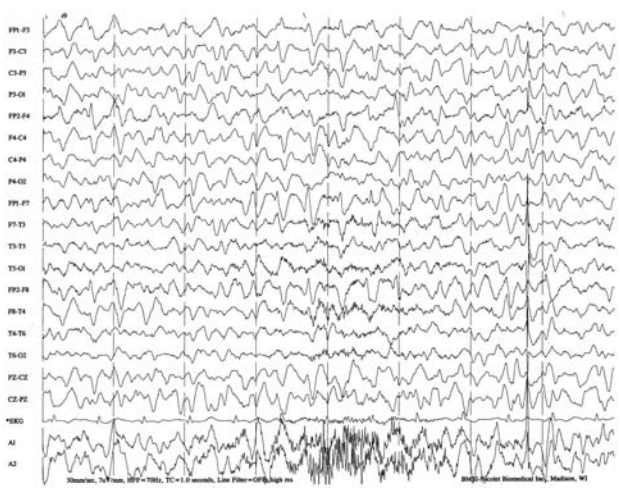

Figure 1 - An EEG recording during non-convulsive status epilepticus.

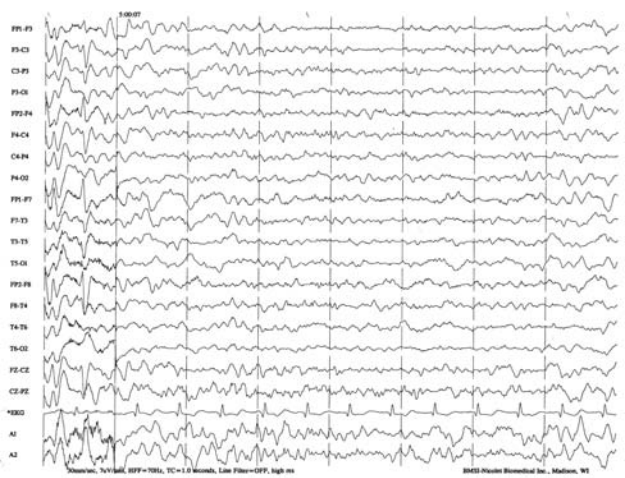

Figure 2 - An EEG after intravenous lorazepam.

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