CASE REPORT

Tiagabine Overdose: A Case of Status Epilepticus in a Non-Epileptic Patient

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Tiagabine is an antiepileptic drug used as adjunctive therapy for partial seizures that is believed to selectively inhibit the presynaptic reuptake of gamma aminobutyric acid (GABA). We describe a case of a tiagabine overdose that resulted in status epilepticus (SE) in a patient without a seizure history. A 14-year-old girl with a history of asthma presented with convulsive SE after ingestion of an unknown amount of her sister’s tiagabine in a suicide attempt. Attempted anticonvulsant therapy included a total of diazepam 10 mg IV, lorazepam 6 mg IV, pyridoxine 5 g IV, and fosphenytoin 20 mg PE/kg. All were without effect. A computed tomography and electrocardiogram were normal. Continuous bedside EEG monitoring showed suppression of seizure activity following intravenous midazolam. A tiagabine level obtained on ED arrival was 420 ng/mL (therapeutic 20–103 ng/mL). The patient was discharged to psychiatry within 1 week with no neurologic sequelae.

Keywords: Tiagabine; Status epilepticus; Overdose

INTRODUCTION

Tiagabine is an antiepileptic drug approved for use as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures. Off-label uses include post-traumatic stress disorder (1), therapy for cocaine dependence (2), and generalized anxiety disorder (3). Although its precise mechanism of action has not been fully elucidated, it is believed to selectively inhibit the presynaptic reuptake of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system (4).

In adolescents 12 years and older, the total daily recommended dose of tiagabine is 32 mg/day while that in an adult is 56 mg/day. Although a therapeutic plasma concentration for tiagabine has not been established, levels of 20–103 ng/mL are reported as the most probable range for seizure control (5).

In February of 2005, Cephalon, the manufacturer of Gabitril (tiagabine HCl), released a drug warning to health care providers stating that the drug may cause new onset seizures and SE in patients without a history of epilepsy (6). To our knowledge, there are currently no reports in the peer-reviewed literature of these events. We report a case of a tiagabine overdose that resulted in SE in a patient without a history of epilepsy.

CASE REPORT

A 14-year-old, 100-kg girl with a past medical history of asthma and taking no medications was found at home unresponsive with tonic-clonic seizure activity. An empty bottle containing a maximum of 90 tiagabine 2-mg tablets and a suicide note admitting pill ingestion were found nearby. The medication reportedly had been prescribed for the patient’s sister for insomnia. During ambulance transport, the patient’s level of consciousness did not improve despite the administration of oxygen, intravenous (IV) diazepam 10 mg, 50% dextrose 100 mL IV, and naloxone 2 mg IV. Her vital signs on emergency department arrival were: blood pressure, 114/83 mmHg; heart rate, 94 beats/min; respiratory rate, 20 breaths/min; temperature, 95.1°F; and pulse oximetry, 98% on 100% oxygen via a non-rebreather face mask. Physical examination was notable for continued unresponsiveness to verbal, tactile, or painful stimuli and intermittent tonic-clonic seizure activity with symmetric limb movements. Unsuccessful attempts to suppress intermittent tonic-clonic seizure activity included the administration of 2 mg lorazepam IV 45 minutes after the administration of diazepam; a second 2 mg IV dose of lorazepam in conjunction with 5 g pyridoxine IV 30 minutes later; a third 2 mg IV dose of lorazepam 2 hours later; and 20 mg PE/kg fosphenytoin IV 6 hours later. Despite pharmacologic therapy, there continued to be no resolution of intermittent seizure activity and the patient did not regain normal consciousness. She was then paralyzed and endotracheally intubated. A computed tomography (CT) of the head was normal as was a 12-lead electrocardiogram (ECG). Laboratory evaluation including serum aminotransferases, sodium, calcium, magnesium, phosphorus, and glucose did...
not reveal any metabolic disturbances. As expected following the therapeutic administration of diazepam, urine toxicology was positive for benzodiazepines. Bedside continuous electroencephalogram (EEG) was initiated 12 hours after patient presentation and demonstrated spike and slow wave discharges consistent with seizure activity. Burst suppression was finally achieved following a loading dose of 1 mg/kg IV midazolam 18 hours after seizure onset. The midazolam was subsequently titrated to 1.4 mg/min IV over a period of 6 hours. EEG monitoring was continued for 72 hours and showed no further seizure activity. Approximately 96 hours after admission, the midazolam infusion was weaned and the patient was extubated. She suffered no neurologic sequelae, and following a complete recovery, was transferred to psychiatric care. A plasma tiagabine level sent on the day of admission for analysis by high-performance liquid chromatography/mass spectrometry was 420 ng/mL (20–103 ng/mL).

DISCUSSION

Following FDA approval of tiagabine as adjunctive therapy for partial seizures in 1997, there have been multiple reports of tiagabine-induced SE in patients with a history of epilepsy (7–12). Although drug administration and seizure activity were temporally related in these patients, it is difficult to determine if SE was induced by the medication or was a result of the epilepsy itself. Interestingly, including the case described above, 59 cases of tiagabine-induced seizures and/or SE in patients without a history of epilepsy were reported to MedWatch between 1997 and 2004 (6). Additionally, although the dose of tiagabine may be an important factor predisposing patients to the onset of seizures, seizures have been reported in patients taking therapeutic doses of as little as 4 mg/day (6).

There are multiple mechanisms that may account for idiopathic epilepsy. Commonly accepted mechanisms include: inhibition of an inhibitory mechanism, enhancement of an excitatory mechanism, enhancement of neuronal burst firing, or any combination of these. Although often unclear, it is generally hypothesized that anticonvulsant medications function by reversal of one of these pathological pathways. For undefined reasons, certain antiepileptic drugs possess the paradoxical ability to increase seizure activity in the epileptic patient at toxic levels. This phenomenon has been previously reported with phenytoin and carbamazepine among others (13). At therapeutic concentrations both phenytoin and carbamazepine inhibit high-frequency repetitive firing through selective slowing of sodium channel closure, thereby preventing initiation of another action potential. It is therefore plausible, in an epileptic patient with underlying pathology, that excessive alteration of sodium channel function occurs at toxic drug levels may account for the increased susceptibility to seizures.

Interestingly, although both phenytoin and carbamazepine toxicity may lead to seizures in patients with epilepsy, only carbamezapine commonly leads to seizure development in the nonepileptic patient (13). To date, there has been only one report of phenytoin-induced seizure activity in a nonepileptic patient (14); however, this patient suffered a ventricular fibrillation cardiac arrest, suggesting that anoxic brain damage may have induced the seizures. It is currently unknown whether the mechanism of anticonvulsant-induced seizures differs between the epileptic and the nonepileptic patient.

Similar to the other anticonvulsants, suggestions specifically as to the cause of tiagabine-induced seizures and SE are ill-defined. A plausible hypothesis may be loss of inhibition due to the depletion of presynaptic GABA available for synaptic release. Richards et al. suggested that excessive GABA-mediated inhibition at GABAB receptors in the thalamus initiates seizure activity in rats (15). Interestingly, this latter theory has been proposed for baclofen-induced seizures (16).

To our knowledge, this is the first case in the peer-reviewed literature of tiagabine-induced SE in a patient without a history of epilepsy.

CONCLUSION

It has been previously documented in the peer-reviewed literature that tiagabine is capable of causing SE in patients with a history of epilepsy. Tiagabine ingestion should also be included, if appropriate, in the differential diagnosis of SE in patients with no prior seizure history when no other cause for new onset seizure can be found. Since tiagabine concentrations are not routinely available, obtaining a medication history for both the patient and other family members may help identify tiagabine as a potential etiology.

REFERENCES
