Tiagabine Overdose Induced Status Epilepticus Responds to Propofol

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Citation

S Haney, B Adams. *Tiagabine Overdose Induced Status Epilepticus Responds to Propofol*. The Internet Journal of Toxicology. 2003 Volume 1 Number 2.

Abstract

Anticonvulsants are the fifth most common source of prescription drug overdose in the United States. However, there is little experience with the newer 2nd generation anti-epileptic drugs. Tiagabine (TGB) is a recently introduced 2nd generation AED for adjunctive treatment of partial seizures. Most toxicology experience with TGB is limited to its chronic use in patients with epilepsy. There are few case reports of acute overdose with TGB described in the medical literature. We present here a further case report of acute TGB overdose presenting as CSE - the second such case in a non-epileptic patient. Our case was unique because the paradoxical seizures were refractory to standard therapy for status epilepticus, but did respond to aggressive therapy with propofol. The literature to date is reviewed. When faced with TGB overdose, clinicians should anticipate status epilepticus and the need for aggressive intervention. If seizures prove refractory to first or second line medical therapy, then high dose propofol should be considered.

Presented at the Southern Medical Association 96th Annual Scientific Assembly, November 15, 2002, Washington, DC

INTRODUCTION

Tiagabine (TGB) is a selective -aminobutyric acid (GABA) reuptake inhibitor that was approved in 1997 for adjunctive treatment of partial seizures.[1] Off-label uses of TGB uses include mood stabilization, sleep disorders, migraine prophylaxis, and neuropathic pain syndromes. Although anticonvulsants are the fifth most common source of drug overdose reported in the United States, there is little acute overdose experience with the newer 2nd generation anti-epileptic drugs (AED's) in general. And in particular, there are only a few reports of acute overdose with TGB described in the medical literature (see Table 1).[2,3,4]

Figure 1

Table 1: Case reports of overdose with tiagabine.

Literature Source	Patient age, sex	Seizure history	History of SE	TGB dose	Co-ingestions	TGB level	Toxicity	Treatment (s)
Damgaard and Friis	adolescent	**	**	400 mg	**	**	CSE	Phenobarbital
Damgaard and Friis	18 months, F	**	**	30 mg	Phenytoin 150 mg	**	Somnolent for 6 hours, tonic-clonic seizure	**
Ostrovskiy et al.	39, M	Absence SGTCS	no	unknown	**	1870 ng/ml	CSE	Lorazepam 8 mg, fosphenytoin 20 mg/kg, midazolam gtt at 7 mg/hour, phenobarbital coma
Ostrovskiy et al	39, M	Absence SGTCS	no	1000 mg	**	2620 ng/ml	CSE	Same patient, same treatment as above
Viner et al	24, M	none	no	52-84 mg (estimated from peak plasma TGB)	**	710 ng/ml at 4.5 hours post-ingestion (est. peak 1180-1974 ng/ml)	CSE	Diazepam 20 mg, midazolam gtt

CPS – complex partial seizures, CSE – convulsive status epilepticus, SE – status epilepticus, SGTCS – secondarily generalized tonic-clonic seizures, TGB – tiagabine, gtt – continuous IV infusion.** Data not reported.

We describe here an additional case of acute TGB overdose presenting as convulsive status epilepticus (CSE), only the second such case reported in a non-epileptic patient. Our case was unique because the paradoxical seizures were refractory to standard CSE therapy. Escalating doses of propofol finally terminated the seizure activity.

CASE REPORT

A 31 year-old male presented to the emergency department in convulsive status epilepticus 30 minutes after ingesting a large (but unspecified) amount of TGB. His past medical history was significant for hypertension, depression, and congenital renal disease requiring renal transplant twice. Besides TGB for mood stabilization and insomnia, his medications were: azathioprine, cyclosporine, prednisone, famotidine, lisinopril, nifedipine XL, calcium, vitamin D, docusate sodium, acetaminophen, and diphenhydramine. There was no historical or clinical evidence of any co-ingestion. Vital signs were: BP = 130/82, HR = 112, RR = 12, T = 36.5 C, SaO2 = 89% on 100% oxygen. He was actively seizing with diffuse myoclonic and clonic activity. The pupils were 5 mm, equal, round and reactive and there was diffuse nystagmus. The rest of the physical examination was unremarkable.

He was intubated and a nasogastric tube and urinary catheter were placed. He was given 50 grams of activated charcoal with sorbitol, and 1 liter of normal saline IV bolus. His ABG on 100% oxygen, just prior to intubation, showed: pH 7.40, pCO2 34 torr, pO2 67 torr, and HCO3 21 mmol/L. The electrocardiogram showed sinus tachycardia with normal QRS morphology, and a chest x-ray suggested mild cardiomegaly. The serum and urine chemistry, toxicology, and hematologic laboratory profiles were otherwise normal except that the cyclosporine was mildly subtherapeutic. A non-contrasted head CT showed no abnormalities. The TGB was 910 ng/ml (upper limits of normal being 234 ng/ml).

First-line treatment with lorazepam 2 mg and midazolam 14 mg IV over 30 minutes had no effect. Phenobarbital at 10 mg/kg IV was administered over 20 minutes also without change in seizure activity. Finally, he was treated with propofol 1.75 mg/kg IV bolus in divided doses over 30 minutes. A continuous IV infusion was begun escalating from 0.9 mg/kg/hour. His seizures finally resolved clinically and by electroencephalogram after titrating to a propofol infusion rate of 3.0 mg/kg/hour. He was weaned off of propofol the next morning and extubated 4 hours later. He was discharged home on hospital day four without apparent sequelae.

DISCUSSION

TGB displays linear pharmacokinetics with 90% oral bioavailability. Peak serum concentrations are achieved in about 45 minutes. TGB is approximately 96% protein-bound, but because its therapeutic levels are in the range of nanograms/ml, it does not significantly compete with other highly protein-bound drugs. It is metabolized in the liver by the cytochrome p450 system, and thus its typical t1/2 of 7-9 hours is decreased by about 50% when co-administered with hepatic enzyme-inducing agents such as phenytoin, carbamazepine, or phenobarbital.[1]

Human experience with TGB overdose is limited. The manufacturer reports 11 patients in the initial clinical trials took single doses of TGB up to 800 mg and experienced only some brief CNS depression.[1] NCSE and SCE provoked by therapeutic doses of TGB are well known.[5, 6] These idiosyncratic cases generally respond to either conventional AED treatment or reduction in TGB dose. Tiagabine is a highly selective GABA-uptake inhibitor. It prolongs the physiologic effects of GABA by inhibiting GAT-1, a membrane-bound GABA-uptake transporter found on presynaptic and postsynaptic neurons and glial cells. The precise mechanism by which TGB overdose may cause paradoxical seizures is not known, but several theories have been proposed. Different brain regions may respond variably to GABA, and excessive GABA-mediated thalamic inhibition by TGB may cause seizures.[3] Differential uptake of GABA by neurons and glial cells may deplete presynaptic intracellular GABA, eventually causing a decrease in synaptic GABA concentrations and failure of GABA-ergic inhibition.[7] GABA-B agonism may exacerbate seizure activity by preventing further release of GABA into the synapse.[6] Finally, the mechanism by which TGB overdose caused refractory status epilepticus in our patient may also be related to its weak affinity for benzodiazepine receptors, and potential for blocking those receptors at high doses.[8]

Up to 10% of SE overall is drug-induced, which is often refractory to conventional AED treatment.[9, 10] First-line treatment for CSE is generally a benzodiazepine followed by phenytoin (or fosphenytoin).[11] Traditionally phenobarbital has been the next line of therapy. Recently propofol has emerged as an alternative. It enhances GABA-mediated synaptic inhibition by binding to distinct sites on the GABA-A receptor-chloride ionophore complex, prolonging chloride channel opening and thus stabilizing post-synaptic membranes. Propofol initially showed anticonvulsant effects in mice treated with various chemoconvulsants.[12] Then successful treatment of amoxapine-induced refractory CSE with propofol in an emergency department setting was subsequently reported.[13] These studies suggest that propofol may be particularly helpful for drug-induced refractory seizures which occurred with our patient. Since delays in

seizure control affects treatment efficacy and clinical outcome, the pharmacokinetic properties of propofol suggest that it may be advantageous for terminating refractory CSE. In a small study comparing outcomes of refractory CSE patients treated with propofol to those treated with high-dose barbiturates, seizure control occurred within 3 minutes with propofol, versus 123 minutes on average with barbiturates.[14] A review of published studies of propofol, midazolam, or pentobarbital for the treatment of refractory CSE found that pentobarbital may be the most effective of the three. But pentobarbital also showed a higher incidence of significant hypotension, often requiring pressor support.[15] Unfortunately the number of patients treated with propofol versus midazolam was too small to allow meaningful statistical comparisons.

CONCLUSION

Status epilepticus should be anticipated with an acute TGB overdose, even in non-epileptic patients. If first and second line therapies fail, propofol should be considered for refractory status epilepticus in TGB overdose. We recommend dosing at bolus 1-2 mg/kg, followed by continuous IV infusion of 1-15 mg/kg/hour, titrated to seizure suppression. However, dosing with this potent drug should be individualized and titrated to the desired effect with particular precaution for respiratory depression and hypotension.

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