Lamotrigine as a possible cause of QRS prolongation in a patient with known seizure disorder

Thomas J.S. Herold, MD, MAJ, MC

ABSTRACT

Lamotrigine and felbamate are 2 newer anticonvulsant medications used to control refractory partial and generalized seizures. Although several cases of lamotrigine toxicity secondary to acute intentional or unintentional overdose have been described, there is little published information related to potential side-effects associated with the therapeutic use of these agents. Described is a case of a 22-year-old woman who presented to the emergency department after experiencing 2 seizure-like episodes. Findings on evaluation included nystagmus, ataxia, widening of the QRS complex and right-axis deviation on ECG. The patient reported only therapeutic use of her medications. The lamotrigine level was 14.8 mg/L. The mechanism of action for lamotrigine is blockade of the sodium channels; therefore, the patient was treated with intravenous sodium bicarbonate with resultant QRS narrowing following administration.

Key words: lamotrigine; felbamate; anticonvulsants; cardiotoxicity; QRS prolongation; tricyclic antidepressant

RÉSUMÉ

La lamotrigine et le felbamate sont deux antiépileptiques plus récents utilisés pour maîtriser les crises d'épilepsie partielles et généralisées réfractaires. Bien que plusieurs cas de toxicité de la lamotrigine secondaire à une intoxication aiguë intentionnelle ou non intentionnelle aient été décrits, il existe peu d'information publiée relative aux effets indésirables possibles associés à l'usage thérapeutique de ces agents. Nous décrivons le cas d'une jeune femme de 22 ans qui s'est présentée à l'urgence après avoir été victime de deux épisodes ressemblant à des crises d'épilepsie. Les constatations lors de l'évaluation incluaient un nystagmus, de l'ataxie, un élargissement du complexe QRS et une déviation axiale droite à l'ECG. La patiente dit n'avoir utilisé ses médicaments qu'à des doses thérapeutiques. Le niveau de lamotrigine était de 14,8 mg/L. Le mécanisme d'action de la lamotrigine est le blocage des canaux sodiques; par conséquent, la patiente fut traitée à l'aide de bicarbonate de sodium intraveineux, qui eut pour effet de provoquer le rétrécissement du complexe QRS.

Introduction

In patients with complicated seizure disorders, therapy with a single commonly used anticonvulsant may not prevent seizures. Combination therapy or the use of uncommon anticonvulsants may be required. The symptoms and signs of the adverse effects that may occur at therapeutic and toxic levels of uncommonly used anticonvulsant agents are not well defined. Lamotrigine exerts anticonvulsant effects primarily via the sodium-channel blockade. Felbamate, which primarily acts as a blocker of excitatory amino acids, also acts by selectively blocking voltage-sensitive sodium channels.[1] The author describes the case of a young woman with long-standing epilepsy on combination

Department of Emergency Medicine, Darnall Army Community Hospital, Fort Hood, Texas

Received: Aug. 23, 2005; revisions submitted: Mar. 26, 2006; accepted: June 20, 2006

This article has been peer reviewed.

Can J Emerg Med 2006;8(5):361-4

therapy of lamotrigine and felbamate who was found to have ataxia and nystagmus, as well as ECG findings that were consistent with a sodium-channel blockade.

Case report

A 22-year-old woman was brought to the emergency department (ED) by bystanders after exhibiting seizure-like activity involving tonic–clonic activity of the upper extremities. No precedent trauma or associated fall was reported. Her belongings were searched, and 2 empty pill bottles were found; one bottle was labelled lamotrigine and the other felbamate.

Physical examination showed a blood pressure of 120/63 mm Hg, heart rate of 140 breaths/min, respiratory rate of 18 beats/min, pulse oximetry of 97% on room air, and an oral temperature of 36.2°C (97.2°F). Initially the patient appeared somewhat somnolent. She opened her eyes to verbal stimuli, conversed but was slightly confused, and was able to localize the source of painful stimuli. She was a thin, somewhat disheveled young woman without obvious physical abnormalities. There was no evidence of loss of bowel or bladder control. Examination of the head, eyes, ears, nose and throat revealed a well-healed, left-sided craniotomy scar. Pupils were equal and reactive, and there was horizontal nystagmus on lateral gaze. Her neck was supple. Cardiac exam was normal except for the tachycardia. The rest of the exam was noncontributory.

Neurologic examination revealed intact cranial nerves, nystagmus as noted previously, 2+ brisk deep-tendon reflexes at biceps and patellar tendons, 5/5 grip strength, absent Babinski reflex, and mild ataxia with wide-based and slightly unsteady gait.

The patient was placed on a cardiac monitor, and an ECG was obtained (Fig. 1). An intravenous (IV) catheter was placed. Basic laboratory studies as well as ethanol, ASA, acetaminophen and lamotrigine levels were drawn. Urine was sent for urinalysis, drugs of abuse (DOA) screening and pregnancy testing. A CT scan was also ordered.

The patient's sensorium slowly cleared, and she was able to provide additional information. She denied any intentional overdose or suicidal ideation, but she was unable to recall the number of pills remaining of each medication. Her past medical history was significant for a seizure disorder since childhood. She reported suffering approximately 3 seizures per week and had undergone a craniotomy for "epilepsy surgery" at the age of 10 years. Her only medications were lamotrigine, 200 mg t.i.d. and felbamate, 600 mg, t.i.d. She smoked a pack of cigarettes per day but denied alcohol or illicit drug use. The review of systems was negative, with the exception of left foot pain secondary to a motor vehicle crash 10 days earlier.

The patient remained hemodynamically stable, and her mental status continued to improve. Her blood glucose level was 6.9 mmol/L (125 mg/dL). Serum chemistry showed a potassium level of 2.9 mmol/L and a negative anion gap. Results of her urinalysis were remarkable only for 1+ ketones and her complete blood count was unremarkable. Ethanol, ASA and acetaminophen levels were undetectable. The DOA screen was presumptively positive for barbiturates. Her ECG revealed a sinus tachycardia, terminal 40 milli-second rightward axis and QRS prolonga-

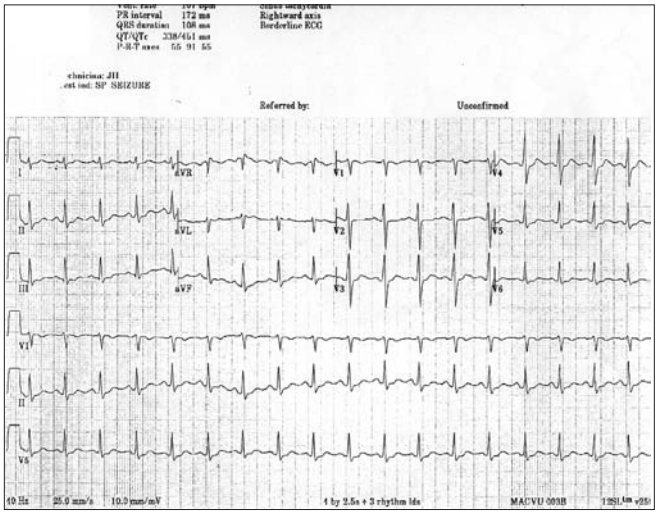

Fig. 1. Results of initial ECG showing tachycardia, rightward axis and QRS duration of 108 ms

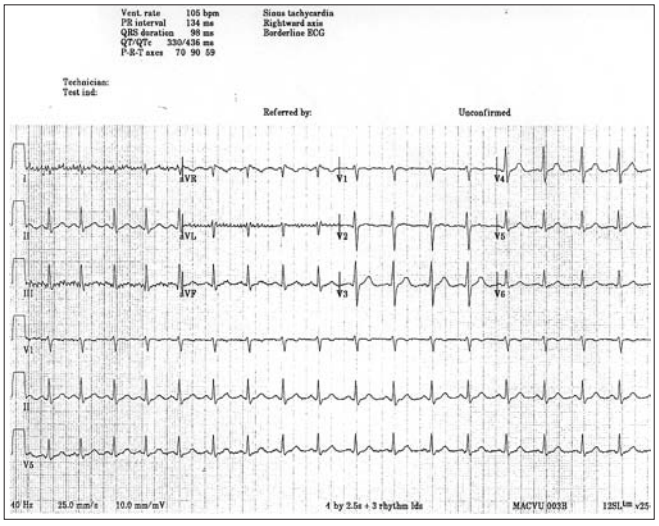

Fig. 2. Results of ECG taken after administration of sodium bicarbonate. Note the QRS duration has decreased from 108 ms to 98 ms. Tachycardia and rightward axis remain.

https://doi.org/10.1017/S1481803500014093 Published online by Cambridge University Press

tion >100 ms (Fig. 1). The CT scan showed the previous left temporal lobectomy, with no acute process. Given the ECG abnormalities, concern for possible tricyclic antidepressant (TCA)–like cardiac toxicity arose. The patient was questioned again regarding all medications or drug use with specific emphasis on use of TCA agents or other antidepressant medications. She adamantly denied a history of depression, TCA use or taking any other medications. A computer-based medication history did not identify any other prescriptions generated from this hospital or its affiliated clinics. Two litres of IV normal saline and 1 ampoule of sodium bicarbonate (NaBicarb) were given. A post-NaBicarb ECG showed persistent tachycardia, but with the QRS prolongation returned to normal (Fig. 2).

The patient's status remained generally stable, with resolution of the tachycardia. Oral and IV potassium replacement was initiated. She had a single episode of seizure-like activity, which consisted of rightward deviation of head and eyes without tonic–clonic movements. A single 2-mg dose of IV diazepam was administered. Her sensorium returned to baseline after an apparent brief post-ictal period. No further recurrence of seizure activity was noted, and the patient requested to be released. She reported having a primary care provider as well as a neurologist. The patient was counselled on risks, with emphasis on the concern for cardiac abnormalities and possible drug toxicity. She was informed that admission and monitoring via telemetry was the preferred disposition. She voiced her understanding, refused admission and was released against medical advice. She agreed to arrange follow up with her neurologist or primary physician the following day. Results of the tests for lamotrigine levels returned several days later; lamotrigine was elevated at 57.8 micromol/L (normal therapeutic range[1] is 3.9–15.6 micromol/L). Prior to this report, the patient was recontacted and her medication profile was reviewed. The patient confirmed dosing and again denied use of illicit substances, TCAs or other medications. She was well before submission of this paper. See Table 1 for sequence of events.

Discussion

The cardiac effects of sodium-channel blockers such as TCAs are well documented. Cocaine, propoxyphene, thioridazine, quinine and some anti-arrhythmics are also sodium-channel blockers and can prolong the QRS complex. The ECG findings in TCA use or overdose include terminal 40 milli-second rightward axis deviation, tachycardia and QRS widening. These ECG changes are due to effects on cardiac voltage-sensitive sodium channels. Lamotrigine has been on the market in the United States since 1993. The mechanism of action is due to inhibition of the release of excitatory neurotransmitters, primarily glutamate, by blocking the voltage-dependent sodium channels, thereby stabilizing the presynaptic membrane.[1] Anticonvulsant effects are believed to be exerted via the sodium-channel blockade.

Felbamate is a newer barbiturarate and exerts its anticonvulsant effects primarily by blocking the effects of excitatory amino acid neurotransmitters, such as glycine, on the *N*-methyl-D-aspartate (NMDA) receptor, thus reducing seizure spread by raising the seizure threshold.[1,2] Felbamate also exerts anti-epileptic action by selective blockade of voltage-sensitive sodium channels.[3] Neither lamotrigine nor felbamate are similar in structure to TCAs (Fig. 3). Most studies conducted evaluating the cardiac effects of lamotrigine report no such effects.[3] However, some investigations have found cardiotoxicity with supranormal serum levels. Dollery's *Therapeutic Drugs* reported an episode of

Table 1. Sequence of events for patient who was brought to the emergency department (ED) after exhibiting seizure-like activity involving tonic–clonic activity of the upper extremities

Event	Time
Patient arrived at ED symptomatic	02:31
Initial ECG obtained*	02:55
Blood work obtained	02:45–04:30
2nd ECG obtained; no change	03:15
Lab results obtained; increased concern for ECG abnormalities	04:55–05:00
Sodium bicarbonate administered intravenously	05:05
Post-treatment ECG obtained†	05:15

*See Figure 1.
†See Figure 2.

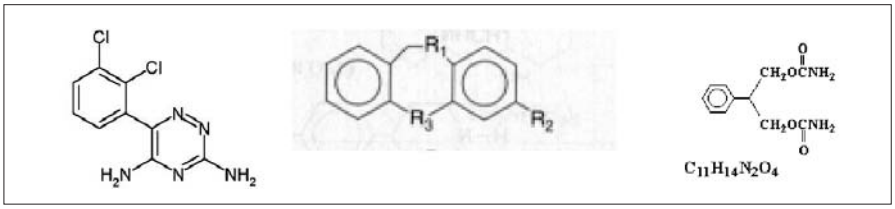

Fig. 3. Structures of lamotrigine, a generic tricyclic antidepressant and felbamate

https://doi.org/10.1017/S1481803500014093 Published online by Cambridge University Press

QRS widening and possible arrhythmogenic risk associated with lamotrigine use.[4] A case report described tachycardia and QRS prolongation associated with an intentional overdose of lamotrigine.[5] Another report described ventricular arrhythmia associated with a mixed ingestion of venlafaxine and lamotrigine.[6] Additionally, a postmortem investigation by Pricone and colleagues found "supratherapeutic" concentrations of lamotrigine in several cases of intentional overdose and coingestion of other medications, particularly valproic acid.[7]

In this case, ECG changes commonly associated with the sodium-channel blocking effects of TCAs were seen. Lamotrigine or felbamate are not known to cross-react with the TCA portion of the urine DOA screen according to the literature provided by the screening test manufacturer,[8] as well as a study evaluating this colloidal immunoassay device.[9] However, TCA-like ECG changes in a patient who is taking a medication known to exert its effect by a mechanism similar to TCAs raises the possibility that the changes are due to that medication. Furthermore, the narrowing of the QRS complex after administration of sodium bicarbonate strengthens this hypothesis. That this patient displayed other signs of lamotrigine "toxicity" (ataxia, nystagmus and elevated serum level) lends credence to the likelihood that lamotrigine was associated with this patient's presentation. Although felbamate has not been specifically implicated in altering the metabolism of lamotrigine, it is not unreasonable to consider that coingestion of these 2 agents may result in elevated serum levels of lamotrigine and contribute to toxicity even when both medications are taken in the prescribed regimen.

In the case presented here, many of the patient's symptoms and findings are consistent with those reported in association with use of these medications. It is more difficult to prove that lamotrigine and/or felbamate was directly causative. In 1965, Bradford Hill outlined 9 characteristics (i.e., strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy) that assist the observer in distinguishing between association and causation.[10] The growing number of cases reported where lamotrigine is described as a contributing factor in adverse cardiac events lends to the strength of association as well as to consistency. Specificity and temporality are supported as well, when one considers that such findings (e.g., ataxia, nystagmus, ECG abnormalities) are identified as occurring in patients exposed to this drug. Other authors' findings support this premise that there is a true biological gradient associated with symptoms and lamotrigine levels.[11,12] Plausibility and coherence are supported by the fact that the side effects documented in the manufacturer's reports are consistent with several of the patient's findings and that the serum drug level was found to be elevated. The characteristic of analogy is supported because other sodium-channel blocking agents (such as TCAs) produce similar ECG effects. If the effect of one drug is known, cause and effect is supported when another drug with a similar mechanism of action produces a similar effect. The only characteristic lacking is that of experimental evidence. There is no, and will likely never be, true experimental evidence defining the threshold of toxicity of lamotrigine or felbamate.

Conclusion

Sodium-channel blocking agents are well known for producing cardiac and neurotoxic effects. No studies have been conducted to determine if lamotrigine, or possibly felbamate, has true "TCA-like" effects on cardiac cells. However, it would seem reasonable to presume that anticonvulsants exerting their neurologic effects via the sodium channel may exert similar toxic cardiac effects as well.

Competing interests: None declared.

References

1. Verrotti A, Trotta G, Morgese G, et al. New antiepileptic drugs in childhood. Panminerva Med 2002;44:221-5.
2. Ticku MK, Kamatchi GL, Sofia RD. Effect of anticonvulsant felbamate on GABA receptor system. Epilepsia 1991;32:389-91.
3. Cohen AF, Land GS, Breimer DD, et al. Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. Clin Pharm Ther 1987;42:535-41.
4. Dollery C, editor. Therapeutic drugs. CD Release 1.0, 1999.
5. Buckley NA, White IM, Dawson AH. Self-poisoning with lamotrigine. Lancet 1993;342:1552-3.
6. Peano C, Leikin JB, Hanashiro PK. Seizures, ventricular tachycardia, and rhabdomyolysis as a result of ingestion of venlafaxine and lamotrigine. Ann Emerg Med 1997;30:704-8.
7. Pricone MG, King CV, Drummer OH, et al. Postmortem investigation of lamotrigine concentrations. J Forensic Sci 2000;45:11-5.
8. Triage drugs of abuse plus TCA [pamplet]. San Diego (CA): Biosite Inc; 1996.
9. Poklis A, Edinboro LE, Lee JS, et al. Evaluation of a colloidal metal immunoassay device for detection of tri-cyclic antidepressants in urine. J Toxicol Clin Toxicol 1997;35:77-82.
10. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300.
11. O' Donnell J, Bateman DN. Lamotrigine overdose in an adult. J Toxicol Clin Toxicol 2000;38:659-60.
12. Briassoulis G, Kalabalikis P, Tamiolaki M, et al. Lamotrigine childhood overdose. Ped Neuro 1998;19:239-42.

Reprint requests and correspondence to: Dr. Thomas J.S. Herold, Department of Emergency Medicine, Darnall Army Community Hospital, 36000 Darnall Loop, Fort Hood TX 76544-4752; 254 288-8302, fax 254 288-8093, HeroldTJ64@aol.com