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CASE REPORT

Lamotrigine-induced seizures in a child: Case report and literature review

JOSEF G. THUNDIYIL, M.D.[1,5], ILENE B. ANDERSON, PHARM.D.[2], PAMELA J. STEWART, M.D.[3], and KENT R. OLSON, M.D.[4]

[1]*School of Medicine, University of California, San Francisco, and California Poison Control System – San Francisco Division, San Francisco, California, USA*
[2]*Associate Clinical Professor, School of Pharmacy, Division of Clinical Pharmacy, University of California, San Francisco and California Poison Control System – San Francisco Division, San Francisco, California, USA*
[3]*Saint Louise Regional Hospital, Gilroy, California, USA*
[4]*Clinical Professor of Medicine and Pharmacy, University of California, San Francisco, Schools of Medicine and Pharmacy and California Poison Control System, San Francisco Division, San Francisco, California, USA*
[5]*Orlando Regional Medical Center, Department of Emergency Medicine, Florida, USA*

Introduction. Lamotrigine is an antiepileptic agent. There is only one previous report of a seizure associated with lamotrigine overdose with laboratory confirmation (a 2-year-old girl, lamotrigine level of 3.8 mg/L). *Case Report.* A healthy 19-month-old boy ingested an unknown amount of his sister's lamotrigine tablets. Twenty minutes later, the child experienced generalized seizure activity lasting 10 seconds, followed by another brief self-limited seizure. Vitals signs: heart rate 152–207 bpm crying, respiratory rate 26 /min, temperature 95.7°F, and pupils 3mm. The one-hour lamotrigine level = 20.3 mg/L. The child was discharged 24 hours later. *Literature Review.* Six previous case reports of lamotrigine poisoning with serum levels, as well as a retrospective review of lamotrigine exposures, are discussed. *Conclusion.* A case of lamotrigine-induced seizures in a pediatric patient is reported, with a level approximately five times the upper limit of the therapeutic range. The pediatric population may be at increased risk of seizures following lamotrigine poisoning, and serum levels may not be clinically useful for predicting outcome after overdose.

Keywords Lamotrigine; Seizure; Pediatric; Poisoning

Introduction

Lamotrigine is an antiepileptic agent that was licensed for use in the United Kingdom (1) in 1991 and in the United States in 1994. It has advantages over other antiepileptic drugs in that it does not impair cognition, inhibit the metabolism of other drugs, and has a good safety profile. However, there is limited information regarding symptoms or management of lamotrigine overdose.

The toxicity of antiepileptics, including lamotrigine, is of particular importance given the increased risk of attempted suicide among patients with epilepsy. Approximately 10% of the population will have one lifetime seizure; estimates of the lifetime prevalence of epilepsy vary from 0.5–4%. Previous studies have shown the suicide rate among the general population to be approximately 1.2%. In comparison, the suicide rate among patients with epilepsy is estimated to be 10 times higher, with an average of 12% (2). This increased rate has been demonstrated among children and adolescents with epilepsy, as well as with adults (3). Although small children are unlikely to attempt suicide, the widespread use and availability of the newer antiepileptic drugs combined with the oral behavior of children, makes them a susceptible population for toxic exposures.

We report a case of lamotrigine-induced seizures in a pediatric patient with a serum level approximately five times the upper limit of the suggested therapeutic range. Additionally, we present a review of the published case reports of lamotrigine overdose.

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Address correspondence to Josef G. Thundiyil, School of Medicine, University of California, San Francisco, UCSF box 1369, San Francisco, CA 94143-1369, USA. E-mail: joseft@mindspring.com

Case report

A previously healthy 19-month-old boy, with no prior history of seizures, was brought to the emergency department 15 minutes after ingesting an unknown number of his sister's 25 smg chewable lamotrigine tablets. In the emergency

department, the child was crying and inconsolable. The heart rate was 152–207 beats per minute while crying, respirations 26 per minute, pupils 3mm, and pulse oximetry 98% on room air. Sinus tachycardia was noted on the cardiac monitor and there was evidence for good perfusion, although no initial blood pressures were documented. Physical examination was unremarkable except for persistent tachycardia and inconsolability. During the child's initial assessment (20 minutes after ingestion), the nurse witnessed generalized seizure activity lasting 10 seconds, followed by another brief self-limited seizure. The child then became increasingly irritable and had multiple episodes of vomiting. No pill fragments were recovered in the emesis. The child was given trimethobenzamide 50 mg rectally, which relieved the vomiting and allowed for treatment with 1 g/kg activated charcoal passed through a nasogastric tube within 90 minutes of exposure to the drug. The child retained the majority of the activated charcoal. Laboratory findings were unremarkable with white blood cell count 12.2 k/mm^3, hemoglobin 11.9 gm/dL, hematocrit 35%, and normal electrolytes (sodium 144, calcium 10.7, bicarbonate 26). The one-hour serum lamotrigine level was sent to an outside lab and 48 hours later revealed a level of 20.3 mg/L (therapeutic range 3–11 mg/L).

The patient was transferred for a higher level of care and further monitoring to a pediatric intensive care unit at a nearby tertiary care hospital. Blood pressure at the time of transportation (4 hours after ingestion) was 92/57 mm Hg. The child had an uneventful hospitalization, and was discharged home 24 hours later. At follow-up one week after hospitalization, the patient was back to his usual state of health.

Literature review

All case reports of lamotrigine intoxication were identified by searching PubMed and by reviewing the reference citations of the pertinent publications. The search terms used included: lamotrigine, lamictal, poisoning, overdose, and adverse reactions. Inclusion criteria included all accidental or intentional cases of acute poisoning. Case reports describing adverse reactions resulting from therapeutic dosing or chronic ingestion were excluded.

Results

Six case reports of acute lamotrigine poisoning (Table 1) and one retrospective analysis (20) were identified through our literature review. Other than our case report, there is only one previously reported seizure as a result of acute lamotrigine poisoning with a documented serum level. That patient, a two-year-old female with no history of epilepsy, ingested an estimated 800 mg of lamotrigine and experienced two seizures that lasted approximately 15 minutes and 5 minutes, respectively (4). The other five case reports involved patients who had a prior seizure disorder, but were not reported to experience seizure activity as a result of the lamotrigine intoxication. Their age ranged from 17–55 years. A review conducted by Lofton and Klein-Schwartz (20) reported seizures in eight out of 493 patients (1.6%) following acute lamotrigine ingestion. None of the cases in their review had laboratory confirmation of lamotrigine.

Buckley et al. reported widening of the QRS complex to 112 milliseconds in a 26-year-old with a lamotrigine level of 17.4 mg/L (5). The QRS interval was normal on a follow-up ECG two months later. No other case reports have demonstrated this phenomenon. Other reported cases of lamotrigine toxicity do not describe hypotension or hypertension.

None of the patients reportedly developed liver or renal injury. Other than the death case involving multiple agents (19), all reported lamotrigine poisonings identified in our review experienced the resolution of symptoms readily with supportive care only. No long-term sequelae were described.

The serum lamotrigine levels in reported lamotrigine poisoning cases ranged from 3.8 mg/L to 35.8 mg/L. Briassoulis reported a 2-hour lamotrigine level of 3.8 mg/L in a two-year-old non-epileptic child who developed seizure activity within one hour after ingestion. Our patient, who also developed seizures within 20 minutes of ingestion, had a serum lamotrigine level of 20.3 mg/L measured one hour after ingestion. In contrast, the three adult patients who did not develop seizures had lamotrigine levels of 32 mg/L (time unknown), 17.4 mg/L (at 3 hours), and 35.8 mg/L (at 5 hours). The 32-year-old man who had a peak measured level of 35.8 mg/L only developed mild neurological symptoms, (6) while a 55-year-old woman experienced encephalopathy with a lamotrigine level of 32 mg/L. (7)

Discussion

We report a case of a 19-month-old boy who developed a 10 second generalized seizure followed by a second brief seizure after accidental ingestion of an unknown amount of lamotrigine tablets. The measured serum lamotrigine level was 20.3 mg/L one hour after ingestion.

The literature surrounding lamotrigine toxicity following acute overdose, especially in the pediatric population, is sparse. However, several adverse affects have been reported in adults with therapeutic use including dizziness, headache, ataxia, diplopia, nausea, hallucinations, nightmares, irritability, and exacerbation of seizures (1,8). Skin rash has been identified as being the most common cause for discontinuation of the medication (9). Additionally there have been case reports associating lamotrigine with hepatic necrosis (10,11), disseminated intravascular coagulation (12), renal failure, ulcerative colitis exacerbation (1), and more severe skin reactions including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. (9) In children, adverse events at therapeutic dosing were shown to be very similar to adults. Side effects included dizziness, tremor, ataxia, nausea, and skin rash. Most of these effects were of mild to moderate intensity

Table 1. Summary of published case reports involving acute lamotrigine poisonings

Reference or case*	Patient & dose	Clinical presentation	Drug levels (mg/L)	Outcome
Case report*	19 mo M unknown lamotrigine dose PMH: none	Irritability, onset of 2 tonic clonic seizures within 1 h. vomiting, HR 152–207, BP nml, RR 26, T 95.7°F, pupils 3mm, pulse oximetry 98% on room air	Lamotrigine 1 hour = 20.3 mg/L	Resolution by 24 hours
4	2 yo M, estimated lamotrigine dose = 800mg PMH: none	Muscle weakness, tonic clonic seizure w/in 1 hr. Hypertonia, 2nd seizure soon after; tremor, ataxia. HR 115, BP 102/50, RR 36. T 36.6°C, EKG nml, pulse oximetry 100%	Lamotrigine 2 hours = 3.8 mg/L (highest)	Resolution by day 2
7	55 yo F unknown lamotrigine dose PMH: seizures ventriculoperitoneal shut	Unresponsive. Normal liver function tests and serum chemistries; Day 3 patient was awake but disoriented.	Lamotrigine = 32 mg/L Valproic acid = 65 mg/L	Awake and alert on day 5
5	26 yo M lamotrigine dose = 1350 mg PMH: temporal lobe epilepsy	At 1 hour: awake, oriented, mild ataxia, horizontal and vertical nystagmus. HR 96, BP 154/90, T 36°C, flushed, QRS 112 msec. Normal liver and renal function tests.	Lamotrigine 3hr = 17.4 mg/L 17hr = 6.4 mg/L	QRS < 100 msec at 2 months
6	32 yo F lamotrigine dose = 4500 mg, with alcohol, clonazepam 2 mg PMH: epilepsy	At 4 hours: awake, staring, slurred speech, ataxic. HR 80, BP 120/80, RR 16, pupils 4–6, pulse oximetry 100%; ECG normal, renal function tests normal. On Day 2: ataxia, rotational nystagmus.	Lamotrigine 5hr = 35.8 mg/L (peak)	Discharged on day 3
18	17 yo F lamotrigine dose = 2000 mg gabapentin 12 grams PMH: epilepsy	At 1 hr: drowsy, slurred speech, Glasgow Coma Scale 15. BP 150/100, HR 100, T 38°C. Dysarthria, motor incoordination, Glasgow Coma Scale 13 within 2 hours.	None available	Resolution by day 2
19	21 yo F PMH: epilepsy, depression	Found dead with a suicide note	Postmortem: lamotrigine = 39 mg/L Also present: ethanol, thioridizine carbamazepine, and paroxetine,	Death: multiple drug overdose

Case refers to our present case report.

(13). In both children and adults, side effects are increased when lamotrigine is used in conjunction with other antiepileptic medications.

The clinical manifestations identified in the two-year retrospective review of lamotrigine exposures reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System included drowsiness/lethargy (20.9%), nausea (5.1%), vomiting (11%), ataxia (4.9%), dizziness/vertigo (4.5%), tachycardia (4.3%), confusion (2.2%), agitation (2.0%), rash (1.8%), slurred speech (1.8%), blurred vision (1.4%), tremor (1.8%), nystagmus (1.6%), seizures (1.6%), respiratory depression (0.6%), conduction disturbance (0.4%), and coma (1.2%). This review included acute and chronic exposures to lamotrigine (20).

Lamotrigine's mechanism of action involves membrane stabilization of neurons secondary to inhibition of voltage-gated sodium channels. These channels play a crucial role in action potential initiation and propagation in nerves and excitable membranes (22). The drug binds to the open and inactivated sodium channel in a voltage dependent manner and induces a conformational change at the pore (21,23). Lamotrigine has been shown to block sustained repetitive firing of sodium dependent action potentials in mouse neurons and rat brains (22). This prevents the release of excitatory amino acid neurotransmitters, particularly glutamate (14). After oral administration, there is nearly 100% bioavailability with maximum absorption occurring between 2 and 5 hours. The volume of distribution (Vd) is approximately 1.3 L/kg (15) with 55% bound to plasma proteins. Interestingly, since our patient's serum level was obtained at one hour after exposure, it is conceivable that the lamotrigine concentration had not yet reached its peak. Fillastre et al. reported that hemodialysis removed approximately 17% of the amount of lamotrigine during 4 hours of dialysis in renal failure patients (16). The elimination half-life varies from 22–36 hours and occurs mainly via hepatic metabolism.

Evaluation of the reported citations in the medical literature suggests that lamotrigine primarily affects the cardiovascular and central nervous systems in overdose. Neurological symptoms are the most commonly reported symptoms

following lamotrigine overdose and include hypertonia, weakness, tremor, incoordination, ataxia, nystagmus, slurred speech, disorientation, stupor, and coma (6,7). Onset of the neurological effects was evident in these cases within 1–4 hours (4,5,6), except for the one case where no time course was described (7). Our patient, as well as the previously reported pediatric patient, both experienced the onset of seizures within one hour of ingestion.

In our patient, only sinus tachycardia was noted on the cardiac monitor. However, considering the fact that lamotrigine blocks voltage gated sodium channels, similar to other cardiotoxic drugs including tricyclic antidepressants, and given the previous case report demonstrating QRS widening and lack of any other substantial data regarding the cardiotoxicity of this drug in overdose, we recommend cardiac monitoring for patients with lamotrigine overdose. Additionally, given the potentially dangerous combination of symptoms in overdose (vomiting, lethargy, and seizures); we recommend use of non-sedating antiemetics and judicious use of activated charcoal with careful attention to airway management.

Previous data has suggested the lamotrigine therapeutic range to be 1–4 mg/L (14). These reports from the literature reveal poor correlation between lamotrigine serum concentrations and clinical symptoms. In a prospective study by Kilpatrick et. al., patients were given escalating doses of lamotrigine until they became seizure free or developed adverse effects. Lamotrigine levels in these patients demonstrated substantial variation in both the seizure-free group (1.4–18.7 mg/L, median 3.8 mg/L) and the adverse event group (0.4–18.7 mg/L, median 4.0 mg/L). The authors concluded that there was no useful relationship between lamotrigine concentration and drug effect or toxicity (17).

Conclusion

There are few reports of acute lamotrigine poisoning. Our case report and review of the available literature suggests that seizures can occur after lamotrigine overdose. Both cases reported to date have had a good outcome following good supportive care in a health care setting. We hypothesize that children may have a higher risk of developing seizures following acute lamotrigine overdose. However, more investigation is needed to evaluate this hypothesis. Management should include cardiac monitoring, treatment of seizures with benzodiazepines, and supportive care. Activated charcoal should be considered for large, recent ingestions. However, when considering activated charcoal administration, precautions should be taken to minimize the risk of aspiration in this patient population considering the risk of sudden onset seizure activity and decreased mental status. Lamotrigine levels do not correlate well with toxicity, have very little clinical value in the overdose setting, and are unlikely to alter patient management.

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