Severe Lamotrigine Neurotoxicity Treated with Intralipid Emulsion Therapy

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Severe Lamotrigine Treated with Intralipid Emulsion Therapy

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Background: Intralipid emulsion (ILE) can be beneficial for cardiotoxicity related to highly lipophilic drugs. [1, 2] Lamotrigine (LTG) is lipophilic; according to the Merck Manual, the solubility of LTG at 25°C is 17 mg/ml in water, 1.9 mg/ml in phosphate buffered saline and 110 mg/ml in intralipid. Lamotrigine neurotoxicity is characterized by multiple coingestants. [3] Severe lamotrigine neurotoxicity treated with intralipid emulsion therapy

Case Report: A 23 year-old male ingested up to 13 grams of LTG and 18 grams of fluoxetine after arguing with his girlfriend. Forty minutes after ingestion, the patient was found slouching and foaming at the mouth. He appeared to have ingested a strong smelling item. A medical history included bipolar disorder, recurrent suicide attempts, posttraumatic stress disorder, Ehlers–Danlos syndrome, and remote plantar fascia surgery. Initial values included 150 mg/dL glucose once daily and 0.1 mg of fluoxetine twice daily. There was no history of tobacco, street drug, or alcohol use.

The patient presented to the outside facility approximately 1 hour after ingestion. Vital signs included a temperature of 33.3°C, blood pressure of 141/58 mmHg, heart rate of 83 beats per minute, respiratory rate of 24/min, and oxygen saturation 99% on room air. The patient weighed 77 kg. The patient was not arousable to noxious stimuli; his GCS was 3/3/3. His left pupil was 6 mm and his right pupil was 3 mm. He was violently thrashing his head and extremities. Laboratory values included a white blood cell count of 9.5, his sodium was 140 mmol/L, potassium was 2.8 mmol/L, chloride was 105 mmol/L, bicarbonate 17 mmol/L, anion gap 18, BUN 12 mg/dL, creatinine 1.2 mg/dL, glucose 228 mg/dL and magnesium 2.1 mg/dL. Liver function tests demonstrated AST 28 U/L and ALT 20 U/L. Venous blood gas values demonstrated a pH of 7.28, PO2 39, PCO2 39, HCO3 11, and base excess of -9. The patient was intubated and ventilated, with a tidal volume of 12 ml/kg and a respiratory rate 14/min. His blood pressure trended down from 141/58 mmHg to 100/45 mmHg, his pulse rate increased from 83 beats per minute to 115 beats per minute and his respiratory rate increased from 24/min to 48/min.

On HD 4, the patient began to raise his head to type and follow commands. He was anxious but did well with independent and learneraptive interaction. The patient then received 4 doses of lorazepam; the etiology was later realized to be benzodiazepine-delirium, not the lamotrigine therapy. On HD 10, the patient became comatose and started to desaturate. This was probably caused by haloperidol and lorazepam as needed. By HD 13, the patient again became restless and agitated, receiving 4 doses of lorazepam over a 6-hour period. In retrospect, the benzodiazepines likely worsened the problem. The patient was transferred to our tertiary toxicology unit, where his Riker agitation scale score decreased from 6 to 3. He blood pressure trended down from 100/45 mmHg to 90/35 mmHg, and his respiratory rate decreased from 48/min to 28/min. On HD 15, the patient became comatose and started to desaturate. This was probably caused by haloperidol and lorazepam as needed. In conclusion, this patient was balancing bacterial growth, inflammatory response, and oxygenation related to aspiration pneumonitis.

Fig 1. a and b: Sedative medication total amounts (mg) and number (n) dose verses time. A 23 year old male ingested 9-13 grams of lamotrigine (LTG) and became hypertensive, tachycardic, confused, and combative. The majority of his dose was spent on HD 2. On HD 2, the patient remained agitated and restless. He experienced impulsive myoclonic jerks and, during a brief restraint follow, fell over the bedrail onto the floor. Although he was not injured, the restraint was removed due to his protection. One dose sulfpramide was started as an adjunctive agent for severe myoclonus. After the second dose, the patient became mildly hypotensive, the haloperidol was discontinued. The patient was then resolved with fluids. His creatinine kinase climbed to 7,771 U/L. An ECG demonstrated evidence of continued sodium channel blockade (see figure 2).

On hospital day 10, the patient continued to struggle when not heavily sedated. He was febrile to 39.6°C. Cultures were collected and vancinamycin and cephalothin were started for presumed aspiration pneumonia. An ECG showed persistent prolongation of the QTc interval from 500 ms in lead I and aVL. The blood sample collected 16 hours post ingestion demonstrated an LTG level of 390 mcg/ml (therapeutic 10-39 mcg/ml). BMAs were taken at that point and reported LTG 20-30 mmol/L, salicylate 17 mmol/L, and non-detectable salicylate and acetaminophen levels. Urine drug screen and comprehensive toxicology tests demonstrated AST 28 U/L and ALT 20 U/L. Venous blood gas values demonstrated a pH of 7.28, PCO2 39, PO2 39, HCO3 11, and base excess of -9. The patient was intubated and ventilated, with a tidal volume of 12 ml/kg and a respiratory rate 14/min. His blood pressure trended down from 141/58 mmHg to 100/45 mmHg, his pulse rate increased from 83 beats per minute to 115 beats per minute and his respiratory rate increased from 24/min to 48/min.

The hypotension resolved with fluids. His creatinine kinase climbed to 1771 U/L. An ECG demonstrated evidence of 4 mm in lead aVR and an S-wave in leads I and aVL (see figure 2). The patient was started on ILE to increase lipid phase and capture free fatty acids, restoring dysfunctional mitochondrial oxidative phosphorylation.[1, 5] Finally, calcium and sodium channel blocking properties may function with ILE.[6] The main known risk associated with ILE therapy is hypoglycemia.[1, 2, 5, 6]

Following administration of ILE, the patient became combative and started to desaturate. This was probably caused by benzodiazepines and dopamine blockade. ILE induces serotonin release, which may temporarily increase levels of serotonin transporters. The result was improved serotonin toxicity, with new unbalanced benzodiazepine antagonism and dopamine blockade, resulting in oversedation. In addition to a deliberately balanced neuroleptic dose of haloperidol, this patient was balancing bacterial growth, inflammatory response, and oxygenation related to aspiration pneumonitis.

Removing serotonin excitation by shifting ILE to intraosoral ILE resulted in significant improvement of blood pressure. One could argue this was the natural course for LTG toxicity. However, our patient's sedation requirements drastically changed from needing 4 doses of lorazepam per day until approximately 12 hours post ILE when he again became restless and agitated, receiving 4 doses of lorazepam over a 6-hour period. In retrospect, the benzodiazepines likely worsened the problem. The patient was transferred to our tertiary toxicology unit, where his Riker agitation scale score decreased from 6 to 3. He blood pressure trended down from 100/45 mmHg to 90/35 mmHg, and his respiratory rate increased from 48/min to 28/min.

Our patient had an apparent initial half-life of 43 hours. The half-life seemed to be prolonged, with a slight increase in LTG concentration may be due to the effects of ILE, pulling LTG from the tissues into the lipid matrix.

In conclusion, this patient's hospital course supports the mechanism of LTG as an inhibitor of voltage-dependent sodium channels, restoring the cardiac action potential's upstroke and repolarization, increasing risk for ventricular arrhythmias and ventricular fibrillation.

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Discussion: This patient's hospital course supports the mechanism of LTG as an inhibitor of voltage-dependent sodium channels, restoring the cardiac action potential's upstroke and repolarization, increasing risk for ventricular arrhythmias and ventricular fibrillation.

REFERENCES:

7. Fagerlund OC and Selkoe DJ (2013) Exercise trials of the University of California San Francisco Medical Toxicology Fellowship: Lamotrigine toxicity (Lamotrigine, Lamictal1).

We present a suicidal patient who ingested between 9 and 13 grams of LTG. The serum level 16 hours later was 348 mcg/ml, the highest level reported in the literature. Not only is this the highest LTG level with survival in the absence of advanced medical care, this is the only report of LTG use for neurotoxicity. This is also one of the only cases of significant LTG toxicity without coingestants.