Severe Lamotrigine Neurotoxicity Treated with Intralipid Emulsion Therapy

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Published In/Presented At

Moore, P., Urquhart, M., McMillion, D., Donovan, J., Burkhart, K., & Cantilena, L. (2012). *Severe lamotrigine neurotoxicity treated with intralipid emulsion therapy.*

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Severe Lamotrigine Neurotoxicity 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 0.17 mg/ml. There are no reports of ILE improving neurotoxicity related to LTG ingestion, however one patient's sertraline and quetiapine induced coma improved after ILE therapy.[3]
Pharmacokinetic data suggest that ILE shifts equilibrium by expanding the lipid phase, capturing and reducing free drug levels.[4] Animal studies suggest that myocardium energy utilization is optimized by the increased circulating fatty acids, restoring dysfunctional mitochondrial oxidative phosphorylation.[1, 5] Finally, calcium and sodium channel function may improve with ILE.[1] The main known risk associated with ILE therapy is hypertriglyceridemia.[1, 2, 5]

Case Report: A 23 year-old male ingested up to 13 grams of LTG and 18 grams of fludricortisone after arguing with his girlfriend. Forty minutes after ingestion, the patient was found shaking and frothing at the mouth. His mother described him as thrashing and tremoring. The patient's medical history includes bipolar disorder with recurrent suicide attempts, postural orthostatic tachycardia syndrome, Ehlers-Danlos syndrome, and remote plantar fascia surgery. Medications include 150 mg of LTG once daily and 0.1 mg of fludricortisone 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 34.6° 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 estimated at 8. 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 2.8 mmol/L, chloride 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, PCO2 39, PO2 55 and oxygen saturation 71%. Other labs included lipase of 33 U/L, lactate 4.3 mmol/L, serum osmolarity of 301 mmol/L, and non-detectable salicylate and acetaminophen levels. Urine drug screen and comprehensive toxicology blood surveys were negative for coingestants. The patient received 2 mg of lorazepam for generalized myoclonic activity and was admitted to the ICU. The myoclonic activity worsened and he received repeated doses of 2-4 mg of lorazepam intravenously. His blood pressure ranged as high as 170/80 mmHg, his heart rate ranged from 90 to110, and his respiratory rate from 25 to 36. Pulse oximetry was 94% on room air and his temperature peaked at 39.4° C. Because of continued difficulties with sedation and agitation, the patient was transferred to our tertiary toxicology unit.

The patient arrived at our institution 11 hours after ingestion. He continued to be hypertensive, tachycardic, and tachypneic, with agitation. There were episodes of moaning and screaming, opisthoclonic posturing, thrashing and myoclonus. Sedatives were administered (see figure 1) and the patient was restrained. Repeated laboratory tests demonstrated an increased AST to 94 U/L. Creatine kinase was 674 U/L. There was an improvement of the anion gap metabolic acidosis as well as creatinine. An electrocardiogram demonstrated a prolonged QRS with terminal R-wave of 4 mm in lead aVR and an S-wave in leads I and aVL (see figure 2).

On hospital day (HD) 2, the patient remained agitated and restless. He experienced impulsive myoclonic jerks and, during a brief restraint holiday, fell over the bedrail onto the floor. Although he was not injured, the restraints were reinstated for his protection. Low dose sublingual clonidine was started as an adjunctive agent for sympathetic mediated sedation. After the second dose, the patient became mildly hypotensive; the clonidine was discontinued. The hypotension resolved with fluids. His creatinine kinase climbed to 1771 U/L. An ECG demonstrated evidence of continued sodium channel blockade (see figure 2).

On HD three, the patient continued to be severely agitated when not heavily sedated. He was febrile to 39.6° C. Cultures were collected and vancomycin, cefepime and metronidazole were started for presumed aspiration pneumonia. An ECG demonstrated persistent prolongation of QRS with elevated R-wave in aVR and S wave in lead I and aVL. The blood sample collected 16 hours post ingestion demonstrated an LTG level of 90 mcg/ml (therapeutic, 3-13 mcg/ml). Because of the high LTG level, continued signs of severe toxicity, worsening rhabdomyolosis, and persistent ECG changes, ILE was administered. A 20% lipid emulsion dosed at 1.5 ml/kg was pushed IV over 2-3 minutes, followed with a 4 hour 0.25 ml/kg/min infusion. His mental status improved; his agitation and restlessness lessened as his Riker sedation agitation scale score decreased from 6 to 3. His blood pressure trended down from 160/70's mmHg to 120/50's mmHg and heart rate from 110 to 90's bpm. Thirty minutes after the ILE therapy, the patient became a Riker 2 and desaturated to the mid 80's which improved with a dose of flumazenil. Three hours after ILE therapy, an ECG demonstrated improved QTc and QRS duration (see figure 2). The patient required one additional dose of lorazepam, 12 hrs after the dose of ILE. LTG levels were monitored (see figure 3). The apparent half-life was 43 hours; the clearance appeared to increase after ILE administration.
On HD 4, the patient began to rouse to his name and to follow commands. He was anxious but did well with haloperidol and lorazepam as needed. By HD 5,he was able to converse but remained disoriented to place and time. He had a gait dysfunction. Antibiotics were narrowed to moxifloxacin as cultures were negative. All sedatives were stopped. On HD 7 he was transferred to a psychiatric facility.

FIGURES

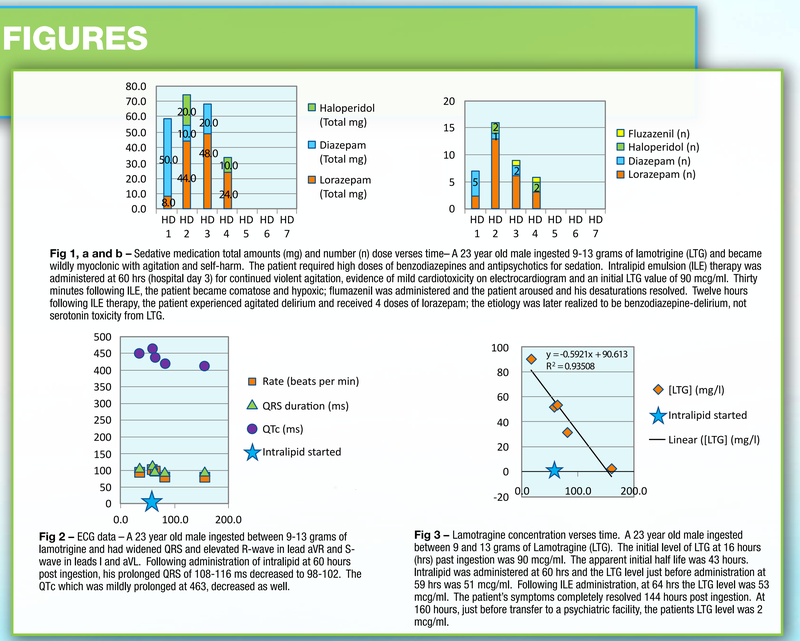

Fig 1, a and b – Sedative medication total amounts (mg) and number (n) dose verses time– A 23 year old male ingested 9-13 grams of lamotrigine (LTG) and became wildly myoclonic with agitation and self-harm. The patient required high doses of benzodiazepines and antipsychotics for sedation. Intralipid emulsion (ILE) therapy was administered at 60 hrs (hospital day 3) for continued violent agitation, evidence of mild cardiotoxicity on electrocardiogram and an initial LTG value of 90 mcg/ml. Thirty minutes following ILE, the patient became comatose and hypoxic; flumazenil was administered and the patient aroused and his desaturations resolved. Twelve hours following ILE therapy, the patient experienced agitated delirium and received 4 doses of lorazepam; the etiology was later realized to be benzodiazepine-delirium, not serotonin toxicity from LTG.

Fig 2 – ECG data – A 23 year old male ingested between 9-13 grams of lamotrigine and had widened QRS and elevated R-wave in lead aVR and S-wave in leads I and aVL. Following administration of intralipid at 60 hours post ingestion, his prolonged QRS of 108-116 ms decreased to 98-102. The QTc which was mildly prolonged at 463, decreased as well.

Fig 3 – Lamotragine concentration verses time. A 23 year old male ingested between 9 and 13 grams of Lamotragine (LTG). The initial level of LTG at 16 hours (hrs) past ingestion was 90 mcg/ml. The apparent initial half life was 43 hours. Intralipid was administered at 60 hrs and the LTG level just before administration at 59 hrs was 51 mcg/ml. Following ILE administration, at 64 hrs the LTG level was 53 mcg/ml. The patient's symptoms completely resolved 144 hours post ingestion. At 160 hours, just before transfer to a psychiatric facility, the patients LTG level was 2 mcg/ml.

Discussion: This patient's hospital course supports the mechanism of LTG as an inhibitor of voltage-gated sodium channels, release of the excitatory neurotransmitters glutamate and aspartate, and serotonin reuptake.[6-8] Persistent ECG abnormalities indicated sodium channel blockade. Serotonin toxicity was manifested by intermittent myoclonus, confusion, tachycardia and hypertension[6, 9]. Other cases of LTG toxicity have been associated with hyperkinetic and hypokinetic movement disorders, seizures, confusion, agitation, hyperthermia, tachycardia, hypertension, hyperreflexia, clonus, prolonged QRS and elevated CK.[8-11] Many reports of LTG toxicity include multiple coingestants. Considering the low toxicity of fludricortisone, this patient's clinical course is attributable to LTG toxicity.

Lamotrigine toxicity is infrequent. The highest reported pre-mortem LTG level was 74.7 mcg/ml in a patient who expired on HD 4 after experiencing seizures, cardiovascular collapse, and persistent neurologic complications.[10] Our patient survived. In addition to this being the highest LTG level reported in the literature, this is one of the only reports of intralipid therapy used for neurotoxicity.

Following administration of ILE, the patient became comatose and started to desaturate. This was probably caused by serotonin, benzodiazepine and dopamine disequilibrium. LTG inhibits serotonin reuptake, causing agitation and other markers of serotonin toxicity. Here, these effects were balanced by high doses of benzodiazepine and antipsychotic agents. Acute shifts of lipophilic LTG towards intravascular ILE were likely miniscule, but enough to restore some of the serotonin transporter. The result was improved serotonin toxicity, with now unbalanced benzodiazepine agonism and dopamine blockade, resulting in oversedation. In addition to a delicately balanced network of neurotransmitters, this patient was balancing bacterial growth, inflammatory response, and oxygenation related to aspiration pneumonitis. Removing serotonin excitation by shifting LTG to intravascular ILE resulted in oversedation and hypoxia.
One could argue this was the natural course for LTG toxicity. However, our patient's sedation requirements drastically changed following ILE therapy. After the desaturation event, the patient was well 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; flumazenil at 22 hours significantly improved his agitation. The remaining anxiety was treated with low dose haloperidol.
The kinetics of LTG is interesting: the concentration of LTG increased slightly after the administration of ILE. Since the peak activity for LTG is within 3 hours, at 60 hours post ingestion, this patient was probably well past peak.[6] The slight increase in LTG concentration may be due to the effects of ILE, pulling LTG from the tissues into the lipid matrix. LTG's half-life is highly variable and 14-103 hours[6, 9]. LTG has can auto-induce its metabolism up to 25%, which is considered clinically insignificant. Our patient had an apparent initial half-life of 43 hours. The half-life seemed to change after the administration of ILE, however more data points are needed to confirm if this change was related to ILE.
We present a suicidal patient who ingested between 9 and 13 grams of LTG. The serum level 16 hours later was 90mcg/ml, the highest level reported in the literature. Not only is this the highest LTG level with survival in the absence of adverse sequelae, this is the only report of ILE use for neurotoxicity. This is also one of the only cases of significant LTG toxicity without comorbid ingestants.

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