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CASE REPORT

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Successful management of massive lamotrigine extended-release intoxication in a dog

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Abstract

A 3-year-old spayed female Siberian Husky presented for evaluation following ingestion of approximately 429 mg/kg of lamotrigine extended-release. She demonstrated severe neurologic and cardiac signs and was treated with lipid emulsion, anticonvulsants, antiarrhythmics and aggressive decontamination and supportive care. She was successfully discharged from the hospital 5 days later.

KEYWORDS

cardiovascular disorders, lamotrigine, neurologic disorders, toxicology, veterinary

1 | INTRODUCTION

Lamotrigine (LTG), a phenyltriazine anticonvulsant drug, is used to treat epilepsy and prevent the recurrence of depressive episodes of bipolar disorder in human patients. While the exact mechanism of action has not been fully elucidated, it is proposed to inhibit the voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and suppressing the release of the excitatory neurotransmitters glutamate and aspartate. This medication is further believed to affect cortical and striatal voltage-activated calcium-gated channels located on the presynaptic membrane. Also, within the CNS, LTG inhibits Cav2.3 (R-type) calcium currents which aid in its anticonvulsant activity and weakly inhibits serotonin 5-HT3 receptors.[1-4] It antagonizes GABA A and B receptors and inhibits kappa and sigma opioid receptors. Aside from the CNS, LTG binds and inhibits peripheral Adenosine A1/A2 receptors, α1/α2/β adrenergic receptors, dopamine D1/D2 receptors, histamine H1 receptors, mACh receptors, and serotonin 5-HT2 receptors.[3] Most recently, LTG has been documented to inhibit cardiac sodium channels at therapeutic doses.[5]

In human patients, LTG has high bioavailability (estimated at 98%) and is rapidly and completely absorbed after oral administration throughout the gastrointestinal (GI) tract with negligible first pass metabolism. The mean volume of distribution of LTG following oral administration in human patients ranges from 0.9 to 1.3 L/kg and is independent of dose administered. LTG is reported to accumulate in the rat kidney, and likely behaves in a similar fashion in humans.[3] Metabolism of the drug occurs in the liver by glucuronidation, predominantly forming 2-N-glucuronide conjugate, a pharmacologically inactive metabolite in humans.[6,7] Other metabolites from glucuronidation include 5-N-glucuronide, and 2-N-methyl metabolite which are formed in significantly smaller quantities in humans.[8] Peak plasma concentrations occur from 1.4 to 4.8 h following drug administration; however, this is influenced by dose.[3] Plasma protein binding is estimated to be 55%, and therefore, it does not interact with other drugs via competition for protein binding sites.[9] LTG is excreted, largely as 2-N-glucuronide, predominantly in the urine, and to far less degree in feces.[3]

In dogs, LTG and LTG XR are extensively metabolized to a 2-N-methyl metabolite, which causes dose-dependent

prolongations of the PR interval, widening of the QRS complex, and at higher doses atrioventricular (AV) conduction block.[10] A pharmacokinetic study in dogs revealed the mean maximum plasma concentration (C_{max}) to be 6.12 ± 2.24 μg/ml, the volume of distribution to be 2.36 ± 1.10 L/kg, and oral body clearance (Cl/F) to be 0.30 ± 0.13 L/h/kg.[11]

There are multiple formulations of lamotrigine, including tablets, chewable tablets, and disintegrating tablets, ranging from 2 to 200 mg. There are also lamotrigine extended-release (LTG XR) tablets available in 25–300 mg strength. LTG XR tablets are film-coated and formulated with modified-release erosion cores. The film has holes drilled throughout to allow for slow release of the drug in the acidic environments of the stomach which in turn allows for a gradual increase in serum levels.[3] Although the pharmacokinetics of LTG is widely unknown in canine patients, if this medication were to be broken and chewed it could lead to a significant increase in serum levels and be more consistent with an immediate-release formulation in human patients. When compared in human pharmacokinetic studies, LTG XR and the immediate-release formulation were similar with respect to steady-state average concentration, area under the concentration-time curve, and trough concentration.[12] LTG XR demonstrated lower fluctuation in concentrations and delayed time to peak concentration (3.0 h vs. 1.3 h). The bioavailability was similar (LTG 73% and LTG-XR 92%). Overall, the formulations were bioequivalent indicating potential 24-hour steady-state benefit of LTG-XR.[12]

All forms of LTG have known interaction with several other commonly co-prescribed anti-epileptic medications (specifically phenobarbital, phenytoin, or carbamazepine).[3] These medications induce glucuronidation which decrease the half-life of LTG, and therefore lower its effectiveness. Human patients on multimodal anti-epileptic medications including LTG require monitoring for recurrence of seizure behavior.[3] These interactions do not seem to play a role in an acute overdose, and generally, symptomatic care is recommended. Close monitoring with discontinuation of the drug is recommended in human patients due to possibility of withdrawal seizures.[3]

The therapeutic dosage of LTG varies if the patient is on other anticonvulsant medications. In adult humans, the starting dose is 25–50 mg every 24–48 h, with the maintenance dose (100–500 mg) reached within 6 weeks.[3] If being prescribed in humans aged 2–12 years old, the dose is based on weight, with starting dose ranging between 0.15 and 0.6 mg/kg/day depending on if they are on other anticonvulsants. The dose is escalated over 3–4 weeks to a maintenance dose between 0.3 and 1.2 mg/kg/day.[3] The most common side effects in humans receiving therapeutic dosages include dizziness, ataxia, and vomiting.[6] More serious side effects that can be seen at therapeutic dosages include serious rash (Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia) and rarely hemophagocytic lymphohistiocytosis.[3,6] In addition, the Food and Drug Administration recently released a safety warning regarding increased risk of cardiac effects in people prescribed LTG at therapeutic dosages.[5] While the effects of LTG on human neurologic disease have been proven to be beneficial, several incidents of accidental and intentional LTG overdose in humans have been reported. A recent systematic review of LTG overdose in adult and pediatric patients resulted in 51 described cases.[13] Consequences of overdose of LTG in humans include seizures, movement disorders, reduced consciousness, arrhythmias (QRS complex prolongation), hypersensitivity reactions, and serotonin syndrome.[14] The majority of exposures only resulted in mild or no clinical signs; however, larger exposure resulted in more significant clinical signs, including cardiac arrest in 6% of exposures. In patients less than 3.5 years of age, ingestion of >525 mg (estimated to be 30–35 mg/kg) resulted in seizures and severe CNS depression.[13]

Standard treatment options for human overdose patients include treatment of seizures with standard anti-epileptic drugs (benzodiazepines, barbiturates, or propofol), sodium bicarbonate, intravenous lipid emulsion (IVLE) therapy, and extracorporeal elimination.[13]

Previous case reports of LTG intoxication have been reported in dogs, ranging from 26 to 278 mg/kg.[15-17] Adverse effects documented included ventricular arrythmias, neurologic abnormalities (including nystagmus and extensor rigidity), and all 3 of the dogs returned to normal between 24 and 72 h. Infusion of intralipids have been found to be beneficial in treatment of LTG intoxication in humans and dogs due to the lipid-soluble nature of the drug.[13,16-19]

This case report describes the therapeutic interventions and successful outcome of a massive overdose of LTG XR in a dog with severe neurologic and cardiovascular sequelae. To the authors' knowledge, this massive overdose of LTG XR is larger than previously described.

2 | CASE SUMMARY

A 3-year-old female spayed Siberian Husky weighing 21 kg (46.2 lbs) presented for an acute onset of hypersalivation and ataxia. Her previous medical history included dietary indiscretion. The owners were out of the house for one hour, and upon return, they found that she had ingested the contents of a pill bottle that contained ninety LTG XR 100 mg tablets. The approximate oral dose ingested was 428.57 mg/kg (194.8 mg/lb). Upon recognizing the ingestion, they immediately began transport to the

hospital (T1). Major clinical signs, therapeutic interventions, and important time points are included in the timeline (Figure 1). Within the 20-minute drive to the hospital, the dog's mentation significantly declined, and she developed generalized seizure activity. On presentation to the hospital (T1.5), she was obtunded, vocalizing, and having generalized tonic-clonic seizure activity. Physical examination disclosed a rectal temperature of 105.2°F (40.7°C), tachycardia (180 beats per minute), and strong and synchronous femoral pulses. She was panting but had normal bronchovesicular sounds on auscultation. Her abdomen was soft and non-painful on palpation. Severe ptyalism was present. Neurologic examination revealed rotary and horizontal nystagmus with the fast phase to the right. Her menace response was absent bilaterally, attributable to her interictal state. She was laterally recumbent and had marked extensor rigidity and opisthotonos.

Initial stabilization and bedside diagnostic testing were performed prior to knowledge of LTG XR exposure due to the severity of the dog's clinical signs. An electrocardiogram (ECG) was performed initially disclosing sinus tachycardia (rate 180–200 bpm); however, multifocal ventricular arrhythmias developed within 2 h after ingestion (Figure 2). A blood pressure via non-invasive methods was initially unable to be determined due to patient's seizure activity. Packed cell volume and total protein were 50% and 6.0 g/dl, respectively. Initial blood gas values (T1.75) are presented in Table 1. An intravenous (IV) catheter was placed, and flumazenil (0.01 mg/kg IV) and naloxone (0.04 mg/kg IV) were administered in an attempt to reverse adverse effects of unknown intoxicants. An IV fluid bolus of a balanced electrolyte solution was administered (10 ml/kg IV over 20 min). Ondansetron (0.3 mg/kg IV) was administered due to marked ptyalism. The dog had conductive (accomplished by dousing with room temperature water) and convective (placement of a fan) cooling, and her rectal temperature was rechecked every 10 minutes. Seizure activity persisted.

At roughly T2.5, it was identified that the patient had consumed LTG XR. Due to the high lipid solubility of the drug, intravenous lipid emulsion (IVLE, 20%) was administered (1.5 ml/kg over 10 min, followed by 0.25 mg/kg/min for 60 min) in an attempt to stop the seizure activity. The dog was continuously monitored during this time and her ventricular arrythmias became more pronounced, with R-on-T waveforms identified. Following treatment with IVLE (T3), she received lidocaine (2 mg/kg IV), which converted her to a sinus rhythm transiently. Due to continued seizures, tremors, and hyperthermia, methocarbamol was administered (100 mg/kg IV over 10 min) at T3.5. In the face of previously administered flumazenil, midazolam (0.5 mg/kg IV) was also administered due to increased seizure intensity but failed to stop her seizures. She was loaded on levetiracetam (60 mg/kg IV), with no effect on the patient's seizure activity. With concern for refractory seizure activity and a potentially lethal dose of extended-release tablets ingested, additional decontamination was deemed necessary, and the decision was made to perform gastric lavage.

The patient spontaneously vomited prior to induction of anesthesia. Ingesta and partially digested, chewed tablets were found, but were unable to be quantified. She received maropitant (1 mg/kg IV) to reduce the risk of continued vomiting while under general anesthesia. At T4, the dog received propofol (2 mg/kg IV to effect) for induction and was intubated with cuffed a 9.5 mm

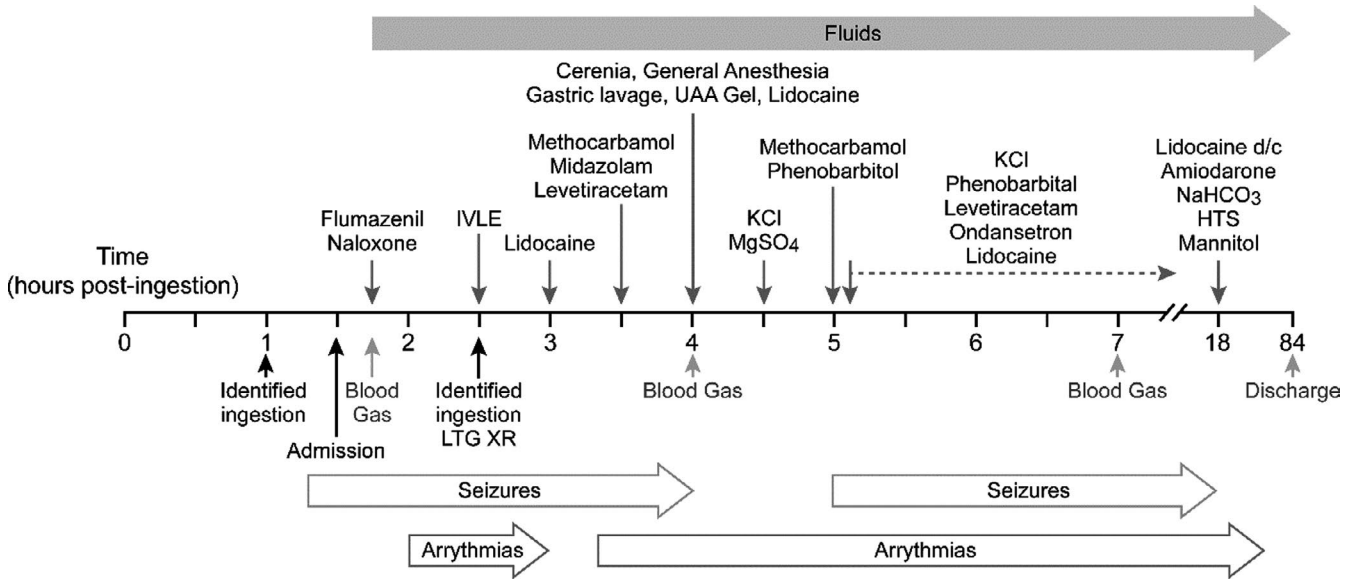

FIGURE 1 Timeline of major clinical signs, therapeutic interventions, and important time points. To represents the time of ingestion

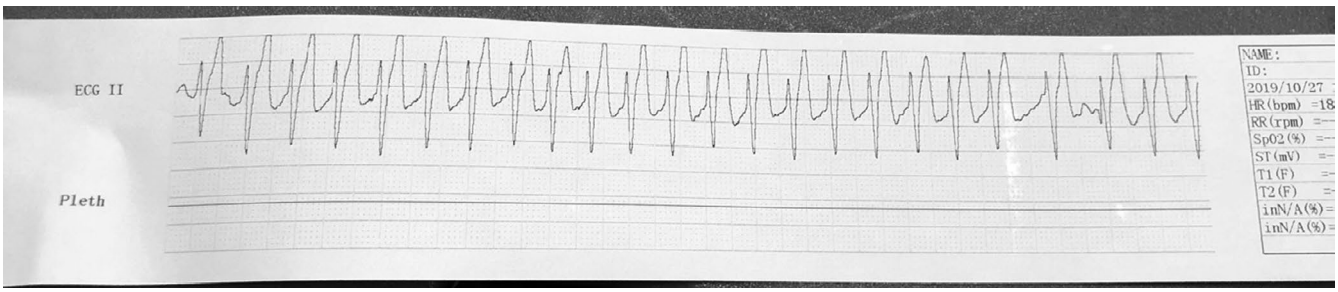

FIGURE 2 Electrocardiogram of patient 2 h post-presentation showing ventricular tachycardia with a rate of 200 beats per minute

TABLE 1 Serial blood gas analysis over time following presentation

Values	T1.75	T4	T7	T18	T24	T42	Reference values
pH	7.354	**7.306**	**7.301**	**7.253**	7.351	7.392	7.35–7.47
$pvCO_2$	31.6	41.9	**53.1**	**45.4**	33.2	**29.8**	32–43 mm Hg
pvO_2	69	68.2	58	66	84	61	30–60 mm Hg
Hematocrit	44	43	**35**	**39**	**34**	**35**	40%–50%
Hemoglobin	14.6	14.2	11.7	13.1	11.3	11.7	8–15 g/dl
Na^+	143.6	145.2	145.0	144.6	**151.3**	137.5	140–150 mEq/L
K^+	3.66	**2.65**	**3.78**	4.18	4.39	**4.94**	3.9–4.9 mEq/L
Cl^-	112.0	111.2	113.2	116.0	**124.0**	117.3	109–120 mEq/L
Ca^{2+}	5.4	5.2	5.3	5.2	**4.7**	5.0	5.0–6.0 mg/dL
Mg^{2+}	1.3	1.2	**1.8**	**1.5**	1.4	1.3	1.04–1.46 mg/dL
Glucose	**273**	**214**	108	107	**140**	**121**	85–112 mg/dL
Lactate	**7.6**	**3.8**	1.6	**5.3**	**2.3**	0.9	0–2 mmol/L
HCO_3^-	17.7	21.1	**26.5**	20.2	18.6	18.3	18–26 mmol/L
Base excess	**−8.0**	**−5.4**	−0.1	**−6.1**	**−7.2**	**−6.9**	(−5)−5 mmol/L
BUN	26	21	17	12	12	15	9.0–33 mg/dL
Creatinine	1.0	0.95	**0.6**	**0.5**	**0.5**	0.8	0.7–1.8 mg/dL

Note: Corresponds to timeline in Figure 1. The bold entries are abnormal values.

endotracheal tube. She was maintained on isoflurane throughout the procedure. No visible seizure activity was seen under general anesthesia. Gastric lavage was performed and numerous partially chewed pills, dog food, and fluid were retrieved from the stomach. The lavage was continued until the effluent became clear. A 12 Fr nasogastric (NG) tube was placed with termination in the gastric lumen confirmed by a lateral radiograph. Activated charcoal (Universal Animal Antidote, Nich Marketers Inc; 3 ml/kg) was administered via the NG tube. Throughout the procedure, the patient's ventricular arrythmias continued requiring an additional lidocaine bolus (2 mg/kg IV), which converted her to a sinus rhythm. A continuous rate infusion (CRI) of lidocaine (50–60 mcg/kg/min) was then started. A blood gas was rechecked at T4 (Table 1). Based on these results, she was started on a potassium chloride CRI (0.5 mEq/kg/hr) for 4 h to correct severe hypokalemia and aid in the treatment of her ventricular arrhythmia. Additionally, she received magnesium sulfate (30 mg/kg IV over 20 min) despite the ionized value being within normal reference range, for additional anti-arrhythmic and anti-ischemic effects on the heart.[20] She was maintained on IV fluids (4 ml/kg/hr) throughout this timeframe.

As the anesthetic plane was lightened, seizure activity and muscle tremors were noted to return. The dog received an additional dose of methocarbamol (50 mg/kg IV) and was loaded on phenobarbital (4 mg/kg IV q30 min × 4 doses) at T5. Over the following hours the patient's temperature, respiration, and heart rate remained normal despite intermittent multiform ventricular arrythmias. Another blood gas was performed at T7 to reassess her electrolytes (Table 1). The dog remained intubated with flow-by oxygen due to lack of gag reflex and stuporous mentation, attributable to anticonvulsant medication administered. She remained on maintenance intravenous fluids, potassium chloride CRI (0.3 mEq/kg/hr), phenobarbital (2.5 mg/kg IV q12hr), levetiracetam (20 mg/kg IV q8hr), ondansetron (0.3 mg/

kg IV q8hr), and lidocaine CRI (50–60 mcg/kg/min). A peripherally inserted central catheter (PICC) was placed in her right lateral saphenous to facilitate medication administration and blood draws. In the ICU, she was closely monitored with telemetry, non-invasive blood pressure, respiratory rate and effort, temperature, pulse oximetry, and end-tidal CO_2 recorded hourly. She also received nursing care, including eye lubrication every 4 h, rotating sides every 6 h, oral care every 6 h, flushing her PICC/IV catheter and aspirating her nasogastric tube every 8 h.

Due to the patient presenting on a weekend during closed laboratory hours, a complete blood count and chemistry profile were performed the first full day of hospitalization on Day 2, which revealed a mild panhypoproteinemia (albumin (28 g/L), globulin (15 g/L), hypocalcemia (2.125 mmol/L), and hypocholesterolemia (2.87 mmol/L)). Oscillometric blood pressure was recorded to be normal (133/78 (93)).

On Day 2, T18, the dog's mentation remained stuporous and minimally responsive and so she was still intubated. She had low-amplitude, high-frequency tremors, mainly of the forelimbs with associated mild extensor rigidity and flaccid hindlimbs. She continued to have rotary and horizontal nystagmus with fast phase to the right. Her ECG showed intermittent ventricular couplets with intermittent R-on-T phenomenon that progressed to runs of ventricular tachycardia, which required additional lidocaine boluses (2 mg/kg IV × 3 doses). The rhythm did not improve, and, in anticipation of starting amiodarone, the lidocaine was rapidly tapered. She was started on amiodarone (2 mg/kg bolus over 10 min, then 0.8 mg/kg/hr for 6 h, and then 0.4 mg/kg/h for 18 h[21]). All other therapies were continued, and a dose of sodium bicarbonate (1 mEq/kg IV over 1 h) was given due to reports of efficacy in treating arrythmias from LTG toxicosis in human literature.[22,23] Administration of bicarbonate resulted in the development of Cheyne-Stokes breathing, bradycardia, and hypertension, leading to concern for elevated intracranial pressure. She received a dose of hypertonic saline (7.5% NaCl 4 ml/kg IV), with no change to vital parameters or respiratory pattern, followed by mannitol (0.5 g/kg IV). This improved her respiratory pattern within about 5 min, but her mentation remained stuporous. Declining mentation in the face of gradual sedation withdrawal over the previous 8 h led to concern for subclinical seizures and complete cortical disconnect; as such an EEG was performed. The EEG was only performed briefly because during placement of electrodes the dog became conscious and began to swallow prompting extubation. As such an EEG was not obtained. Her heart rate and rhythm improved on the existing anti-arrhythmic therapy. Her mentation was also improved such that she ate well when offered food. She was noted to have black, soft stool, consistent with passing activated charcoal.

On Day 3 (T42), she was alert and responsive with a normal cranial nerve examination. Her vitals were normal. She remained recumbent and unable to ambulate; however, her postural reactions were improved. She had bloodwork performed to check her electrolytes and acid-base status, which remained within normal limits (Table 1). She continued similar supportive care for an additional 24 h and was able to be transitioned to oral medications on Day 4 of hospitalization. She continued to remain cardiovascularly stable and was neurologically improved. By Day 4, (T66) she regained her ability to ambulate and was able to meet nutritional needs on her own. She was discharged on Day 5 (T84) with the following oral medications: levetiracetam XR (23 mg/kg PO q12hr), phenobarbital (2.3 mg/kg PO q12hr), mexiletine (3.5 mg/kg PO q8hr), and amiodarone (4.76 mg/kg in the morning and 2.4 mg/kg in the evening).

The dog was rechecked 2 weeks following discharge for placement of a Holter monitor. She had no documented arrhythmic events over 24 h while her monitor was in place. Her anti-arrhythmics were therefore discontinued one month after initial discharge. She had another Holter placed 2 weeks after the anti-arrhythmics were discontinued and again had no documented events. She was able to be tapered off of her anticonvulsants within three months of discharge, and at most recent follow-up has had no additional seizure activity.

3 | DISCUSSION

Lamotrigine is not used in veterinary medicine; therefore, there is very little information regarding its pharmacokinetics. Studies in laboratory animals have documented an LD50 of 245 mg/kg and 205 mg/kg in mice and rats, respectively. In dogs, however, LTG is metabolized in the liver to a toxic metabolite LTG-2-N-methyl, by a species-specific methyltransferase, prior to elimination by the kidneys. This metabolite causes severe cardiac disturbances in a dose-dependent manner.[10] Only trace amounts of the 2-N-methyl metabolite have been documented in human urine; therefore, these effects are not commonly seen in people.[3,10]

Life-threatening clinical signs have been observed in dogs and cats at much lower doses. The ASPCA Poison Control Center reports lethargy, vomiting, and somnolence at doses as low as 5 mg/kg, agitation, ataxia, tremors, and tachycardia at doses of 16 mg/kg and higher, and seizures, hypotension, tachy- or bradycardia, arrythmias, vocalization at doses of 37 mg/kg and higher.[10] The exact fatality rate for veterinary patients ingesting LTG

or LTG XR is not known. As previously reported, review of the ASPCA Poison Control Center's database from 2003 to 2011 showed a fatality rate of 7% in dogs (9/128 cases) with known or highly suspected LTG ingestion.[10] Unfortunately, long-term follow-up was not possible in the majority of dogs (74%) so this number may be underestimated. Of those who were reported to have died after ingestion, one was seizing at home and died without medical attention, two were found dead at home, two were euthanized while receiving treatment and five dogs arrested suddenly, suspected to have had fatal arrhythmias.[10] One of these cases was a 1.5-year-old Labrador retriever who ingested 67.8 mg/kg and displayed ventricular arrhythmias and bundle branch block prior to arresting.

There are a few case reports of LTG intoxication in canine patients. A report of a 2-year-old English Bulldog who ingested LTG 26 mg/kg displayed a dull mentation and ventricular tachycardia. This patient was given IVLE and was discharged to home in 72 h.[16] A more recent case report documented a 1-year-old dachshund/mixed breed dog who ingested LTG 135–162 mg/kg and displayed neurologic and cardiovascular effects that also responded well to IVLE. Additionally, IVLE therapy led to a significant decrease in measured serum lamotrigine levels.[17] The patient was discharged after 38 h in the hospital with normal physical and neurologic examinations. A report of a 7-month-old Labrador retriever who ingested 278 mg/kg of LTG XR displayed both neurologic and cardiovascular effects, all of which resolved within 24 h with minimal treatment required; IVLE was not administered.[15]

The dog reported here received 1.5 times the dose of the previously highest reported LTG XR overdose.[15] Despite aggressive gastric decontamination, the dog was presumed to have ingested a dose (1.7×) higher than the LD50 documented in other species, and eleven times the documented dose of symptomatic patients. While LTG XR and standard LTG formulations are reported differently, previous canine research supports that the pharmacokinetics of these products is similar, and therefore, comparison is possible.[12]

Ranging from 0.9 to 1.3 L/kg, LTG is considered to have a large volume of distribution (Vd), is 55% protein bound, and has a 1.4 partition coefficient (logP).[3] The Vd of LTG would indicate that the patient in this report would have had wide distribution throughout the body, that could have prolonged the anticipated half-life of the effect of this medication. In some circumstances in human medicine when the Vd is high, saliva levels of drug can be measured to determine efficacy of decontamination and excretion. However, it has previously been determined that Vd of LTG and LTG XR is dose independent, and the rate of clearance from the body would have been the same (independent of dose).[24] As this is not available, and likely unnecessary for treatment interventions, this was not pursued in this case. When using IVLE in cases of intoxication, data show that emergent use should be determined based on both the volume of distribution and partition coefficient of medications. Based on linear regression models in humans, it has been predicted that there would be a 2% decrease in serum levels when IVLE is given for lamotrigine toxicosis.[3] This study also found a wide variability among lamotrigine models. IVLE is considered a last resort; however, based on the severity of clinical signs noted in this patient and the positive response to IVLE in previous case reports, the decision was made to administer to this patient.

Current standard of care following toxin ingestion includes decontamination, reducing gastric absorption and symptomatic care. Gastric decontamination via emesis (naturally occurring) and gastric lavage was performed in this case due to the rapid onset, severity and progression of clinical signs, dose ingested and potential for prolonged gastrointestinal absorption. Further absorption was reduced through the use of activated charcoal. In humans, LTG is primarily renally excreted (94%), with elimination half-life in non-uremic humans being around 25 h.[3,25] In patients with renal dysfunction, elimination half-life is significantly longer. In addition to gastric decontamination, fluid therapy is also a mainstay of treatment to promote renal excretion. Patients who exhibit signs of renal insufficiency are good candidates for urine output quantification, careful fluid diuresis, and potentially hemodialysis. The patient described here did not exhibit evidence of acute kidney injury so an indwelling catheter for urine quantification was not placed. However, an indwelling urinary catheter could have been considered in this case to prevent transluminal reabsorption of cleared drug.

At the time of presentation, the initial information was that the dog had consumed anticonvulsant medication; the exact medication was not known. Therefore, the common benzodiazepine reversal agent flumazenil was administered. Naloxone was administered as the patient's mentation was markedly abnormal, and it was assumed that the dog could also have been narcotized. Once the intoxicant was identified as LTG XR, a more targeted therapeutic approach was performed. An infusion of intralipids has previously been shown to be successful in other cases of LTG toxicosis in both dogs and humans due to the lipid-soluble nature of LTG.[13,16-19] The standard dose used for most veterinary toxicities treated with IVLE is to give an initial bolus of 20% IVLE of 1.5 ml/kg over 1 minute, followed by a CRI of 0.25 ml/kg/min for 1 h.[26] Depending on the patient's response, the toxin ingested and evidence of serum lipemia, the bolus dose and CRI may be repeated every 4–6 h for up to 24 h. Anecdotally, if the patient's

serum remains lipemic prior to administration of the next scheduled dose, repeating the dose may not be as efficacious and may predispose the patient to negative sequelae, such as hemolysis, hypertriglyceridemia, and anaphylactoid-like signs, among others.[26] In the case described here, an additional dose of IVLE was not given 6 h after the first dose administered because her serum was still lipemic when re-evaluated. In addition, the patient was still exhibiting severe ventricular arrhythmias, and there was concern that re-dosing the IVLE would further impact the efficacy of the anti-arrhythmics.

While IVLE treatment has been proven to be beneficial for patients with LTG, a significant clinical concern is that many of the other therapeutic medications needed to treat the sequelae of the overdose are lipid-soluble as well. In this case, midazolam was used as a first line anticonvulsant therapy. It is possible that the effectiveness of this medication was decreased due to previous flumazenil administration; however, it is also possible that both flumazenil and midazolam had initially decreased efficacy due to their lipid solubility at physiologic pH.[27,28] Similarly, initial attempts to control ventricular ectopy with lidocaine may have been impaired by the use of IVLE. The first use of IVLE in the literature was for treatment of local anesthetic toxicity, specifically bupivacaine, which has a similar mechanism of action and lipid solubility as lidocaine.[29] While initial decreased efficacy of these medications may be attributed to IVLE therapy, the seizure activity and cardiac arrhythmias were sustained several hours after initial IVLE treatment. This patient's seizures and muscle tremors were refractory to standard therapy (midazolam, levetiracetam, phenobarbital, and methocarbamol) and required aggressive loading of these medications over a short period of time. Due to the persistence of lipemia, it is possible that IVLE therapy may have limited the effectiveness of phenobarbital and methocarbamol.[26] Owing to the presumed decreased efficacy, dose adjustment of these medications could have been considered to increase efficacy. Side effects of all of these medications are sedation, which may have contributed to the patient's stuporous status on Day 2 of treatment, conflicting with the theory that their results were mitigated by IVLE.

While the decision to administer IVLE is based on the lipid solubility of a potentially toxin exposure in the hopes of reducing clinical impact, there have been reports of IVLE increasing the serum levels of a medication by acting as a "reverse sink."[30] Based on the persistence of clinical signs after IVLE administration, it is possible this was playing a role in this case. This may have been due to time of ingestion of the drug and then timing IVLE administration. If the medication had not yet been fully absorbed, administration of IVLE may have led to increased absorption from the GI tract into bloodstream, thereby increasing serum levels of the drug. Thus, it is important to know timing of ingestion to best determine treatment options.

The development of muscle tremors in this patient is likely associated with serotonin syndrome due to the massive overdose of LTG XR. LTG is a serotonin reuptake inhibitor, allowing for higher serotonin (5-hydroxytryptamine [5-HT]) to be present in the synaptic cleft. Serotonin is a neurotransmitter that is released into the synapses of nerve cells. It is present in health and disease and the manipulation of serotonin receptors helps to treat multiple neurologic and systemic diseases.[31] Serotonin syndrome is a syndrome caused by overactivation of central and peripheral 5-HT receptors. While previous serotonin syndrome research implicates the 5HT-1A and 5HT-2A receptors are the most commonly affected, seven families of 5-HT receptors exist.[32] Different receptor families have different functions, but are generally either excitatory (5HT-2, 5HT-3, 5HT-4, 5HT-6, and 5HT-7) or inhibitory (5HT-1 and 5HT-5). At standard dosing, LTG weakly inhibits 5HT-3 receptor. At massive doses such as in this report, it is possible that blockade of 5-HT receptors could result in significantly increased serotonin levels in the synaptic cleft. LTG has been implicated in life-threatening serotonin syndrome following overdose in humans.[33] Patients demonstrate a variety of clinical signs with serotonin syndrome including (but not limited to) agitation, disorientation, restlessness, excitement, tremors, clonus, muscle rigidity, hypertension, tachycardia, tachypnea, hyperthermia, vomiting, and shivering. Serotonin syndrome itself can be fatal.[32] The dog in this report demonstrated many of these signs. Given the refractory nature to standard therapy, serotonin antagonists such as cyproheptadine could have been considered. Cyproheptadine is supplied in an oral formulation which makes administration in mentally inappropriate patients challenging; however, administration through her previously placed NG tube, or given rectally, could have been considered.

Magnesium supplementation has been shown to be beneficial in reducing the rate of ventricular and supraventricular arrhythmias in human patients. A recent metanalysis of the effect of magnesium supplementation on patients following acute coronary syndrome showed a significant decrease in both ventricular and supraventricular arrhythmias compared to placebo.[34] Magnesium is an essential electrolyte for a number of biologic processes. It is a cofactor of the cell membrane sodium-potassium (Na-K) pump and participates in many enzymatic reactions.[34] Magnesium deficiency reduces the amount of intracellular potassium and activity of the Na-K pump, which ultimately disturbs the resting membrane potential of cardiac myocytes, leading to arrythmias. Given the proclivity of

ventricular tachyarrhythmias, and refractory response to treatment, supplemental magnesium was administered. In conjunction with LTG directly causing hypokalemia due to inhibitory effects on A-type potassium current in hippocampal cells, supplementation of potassium and magnesium was given.[3,35]

There are numerous case reports describing the administration of sodium bicarbonate to treat the QRS prolongation seen in cardiotoxicity with LTG.[13,19,23] Lamotrigine's effects likely block the fast sodium channel, slowing conduction during the phase 0 upstroke of the action potential, resulting in QRS widening. In previous studies, transient improvement in cardiac conduction has been noted following sodium bicarbonate administration. This blockade is similar to tricyclic antidepressants, which is an indication for alkalinization of the blood via bicarbonate administration, which results in a decrease in the ionized portion of the drug, reducing the toxic effects.[19] In a recent metanalysis, there were 51 human case reports meeting their inclusion criteria, of which only 10 cases (20%) received sodium bicarbonate for treatment of conduction delays, showing only a transient or negligible response.[13] In the present case, this therapy was withheld on the day of presentation due to the presence of a respiratory acidosis. On Day 2, the dog remained refractory to standard ventricular arrhythmic management (lidocaine, amiodarone) and a dose of sodium bicarbonate was given.

Cheyne-Stokes breathing is a respiratory pattern described by periods of hyperpnea followed by periods of apnea and is generally seen in patients with diffuse cerebral or thalamic disease. It may also be seen in patients with metabolic encephalopathies, which is a possible cause for the respiratory pattern in this patient. Alkalinization of the blood may have led to hypocalcemia due to redistribution, causing an acute change in the respiratory pattern in this patient. Unfortunately, a blood gas was not repeated just after administration of sodium bicarbonate and development of this breathing pattern in this patient, so the exact mechanism is unclear.[36] Another consideration for the development of this respiratory pattern would be due to paradoxical central nervous system (CNS) acidosis. Paradoxical CNS acidosis occurs following rapid bicarbonate administration due to a decrease in pH in the cerebrospinal fluid.[37] This phenomenon occurs because the blood-brain barrier is permeable to carbon dioxide, but less permeable to the bicarbonate ion due to its negative charge. With administration of sodium bicarbonate, the pH in the extracellular fluid increases and compensatory hyperventilation decreases, which would affect the respiratory rate of the patient. With an increase in partial pressure of carbon dioxide, carbon dioxide will diffuse into the CNS in excess of bicarbonate, leading to a decrease in the cerebral interstitial and intracellular pH.[37]

This case report has some limitations. As mentioned previously, the administration of IVLE likely reduced the serum concentrations of anti-arrhythmics (lidocaine and amiodarone) and anticonvulsants (midazolam, phenobarbital) needed to control the patient's clinical signs. This is a commonly encountered issue with toxin ingestion. At the time the case was being managed, we felt the benefit of IVLE administration outweighed the risk of therapeutic drug attenuation in this patient, given previous documentation of favorable outcomes.[15-19] Further studies are needed to determine the efficacy of IVLE administration in LTG XR intoxication.

The recommended dose of activated charcoal is 1–5 g/kg.[38] The patient described here received the dosage listed on the manufacturer's packaging for the formulation used at the author's institution (3 ml/kg). As a result, the amount given (360 mg/kg) is lower than the recommended dose. Administration of activated charcoal requires an individual patient risk-benefit assessment. Due to the patient's abnormal neurological signs and the large amount of volume that would have been required for this patient (1 g/kg = 208 ml), a more conservative volume was administered to prevent further aspiration events. The fact that activated charcoal is the most effective when provided within the first hour of exposure, and efficacy decreases outside of this window,[39] was also considered in the risk-benefit of volume administration. Efforts were directed at other forms of decontamination that reduced the patient's risk for acquiring additional complications (eg, aspiration pneumonia). However, if this dose is subtherapeutic, it might have contributed negatively to prolonged clinical signs observed in this case. While a single dose of activated charcoal has been shown to significantly reduce concentration-time curves of LTG in a study of healthy human volunteers,[40] it is possible that repeated doses of activated charcoal at therapeutic levels may have been beneficial in this patient.

This patient's lab work was mostly normal, likely owing to the absence of other significant medical co-morbidities. On initial presentation, the most significant blood gas abnormalities were hyperglycemia and hyperlactatemia, most likely due to her tremor and seizure activity. These values improved with initial fluid resuscitation. Electrolytes were serially monitored and supplemented as needed. While it might not have changed the treatment, evaluation of LTG presence in the serum was not available. Serum LTG may have allowed us to serially monitor response to IVLE treatment as previously described.[17]

Lastly, the option of hemodialysis for treatment of severe LTG has been considered and performed in humans with LTG overdose.[41] One report showed reduction in LTG half-life with dialysis, with the LTG extraction factor reported to be 17%–20%.[41] The reports of extracorporeal

therapies (IHD and hemoperfusion) seem to be associated with patients who have prolonged neurologic deficits that are refractory to standard therapies. Dialyzability of a medication is determined by multiple factors: small molecular weight (<2000 Daltons), not highly protein bound, (less than 80% preferred), highly water soluble (hydrophilic), and small volume of distribution (<1–2 L/kg; dialyzes drugs from blood, not fat, bones and tissue).[42] LTG has a low molecular weight (256.09 Da), is not highly protein bound (65.7%), and has a moderately large volume of distribution.[3] Hemodialysis was considered as a therapeutic option for this patient, and this could have potentially led to a decrease of the medication below toxic levels in the blood. A possible concern with this option is the potential of redistribution from tissues after the medication has been removed from the blood, and so might not have a significant impact on clinical signs secondary to toxicity. While this modality is available at our institution, the reports of success with hemodialysis in humans are variable and given the relatively high cost of that treatment compared with others provided, that was not pursued for this patient. Had her neurologic status remained severely impaired, this therapeutic modality may have been pursued.

4 | CONCLUSION

This case highlights the rapid onset of clinical signs and aggressive decontamination and supportive care required for a patient who received a massive LTG overdose. Previously documented beneficial effects of IVLE in LTG intoxication were not evident in this case. Further studies are warranted to determine whether routine use of IVLE should be included in the management of LTG intoxication in the dog. Despite severe refractory cardiac and neurologic abnormalities and initial dependence on anticonvulsants and anti-arrhythmics, this patient was able to be tapered off all medications within 3 months of ingestion.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
ASM, AAY, and ESC managed the patient. ASM, PEY, ESC, and AAY wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

ETHICAL APPROVAL
The authors confirm this patient was treated with current standard of care in veterinary medicine and to the best of their abilities. As this was a retrospective case report, approval by a licensing board was not required.

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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