Lamotrigine: human medication toxic to pets

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Lamotrigine (Lamictal, GlaxoSmithKline), a phenyltriazine compound – 1,2,4–triazine-3,5-diamine, 6- (2,3-dichlorophenyl) is a second-generation antiepileptic drug used for the treatment of partial and generalised seizures as well as bipolar affective disorder in human medicine[1].

Lamotrigine (LTG) is prescribed for oral administration as regular, chewable dispersible, orally disintegrating, and extended-release tablets[1,2]. Retrospective case series from 2003 to 2012, have studied the clinical manifestations of humans exposed to LTG in overdose[3]. LTG toxicity was associated with minor to moderate neurologic effects and/or cardio toxicity symptoms to some degree in the majority of patients[3,4]. Rare serious effects have been reported[3,4].

A review of the American Society for the Prevention of Cruelty to Animals' database from 2003 to 2011 identified 138 LTG cases involving 128 dogs and 10 cats5. Eight of the 138 animals (6%) died due to the exposure[5].

Pets can accidentally ingest medications for their human owners. Ingestion of LTG by pets is a life-threatening emergency and veterinarians should be aware of the high toxicity of this human medication to pets[6].

Pharmacokinetics

LTG is a weak basis (pKa 5.7), lipid soluble (logP 2,4)[1,7]. The pharmacokinetics of LTG is linear, and can be described as a one-compartment model[8,9].

Absorption

Following oral administration, LTG is rapidly and completely absorbed from the gastro-intestinal tract with negligible first-pass effect[1,7]. The absolute oral bioavailability is 98% and is unaffected by food[1,7]. The peak plasma concentration occurs at one or one-and-a-half hours with the immediate-release formulations and four to 11 hours with the extended-release formulations[1,2,6]. Serum concentrations of LTG increase in direct proportion to the dose ingested[8,9].

Distribution

In the blood, LTG is approximately 55% bound to serum proteins[1,7]. The mean apparent volume of distribution ranges from 0.9L/kg to 1.3L/kg[1,7]. LTG binds to melanin and it could accumulate in melanin-rich tissues (eye and pigmented skin)[1].

LTG distributes into saliva in humans[10], salivary LTG concentrations being on average 0.4 to 0.5 that of serum concentrations, which makes saliva an interesting sample to perform toxicological analysis[10]. LTG crosses the placenta in rabbits[1].

Biotransformation

In dogs, LTG is metabolised in the liver predominantly to a LTG-2-N-methyl[1]. This metabolite causes severe cardiac disturbances in a dose-dependent manner[1].

Only trace amounts (0.14%) of the LTG-2-N-methyl have been found in human urine[1,9,11]. LTG is also metabolised in dogs by glucuronic conjugation at the two-position of the triazine ring (2-N-LTG glucuronide)[12].

Elimination

Elimination of LTG is essentially renal, with 94% of the drug excreted through the urine and 2% excreted in the faeces[1,13]. Mean plasma elimination half-life (t1/2?) is 22.8 hours to 37.4 hours on single oral dose administration[13]. The pharmacokinetics of LTG is not affected by renal impairment[13].

Pharmacological properties

LTG inhibits voltage-sensitive sodium channels, thereby stabilising presynaptic neuronal membranes that may result in a decreased release of the excitatory amino acid neuro-transmitters (glutamate and aspartate)[1,8].

LTG may have also potassium channel-blocking actions by bindings to hERG (human Ether-a-gogo-Related Gene) potassium channels[14]. hERG encodes the cardiac rapid delayed rectifier ion potassium current, I_{Kr}, in atrial and ventricular myocytes[14,15,16,17]. LTG inhibits the current I_{Kr}, which is crucial for repolarisation of cardiac action potentials[16,17].

Risk assessment

The oral median lethal doses (LD_{50}) of LTG are 245mg/kg and 205mg/kg in mice and rats respectively[1,7].

In dogs, doses of 3.4mg/kg of LTG induce lethargy and somnolence6. Cardiac signs are generally

not seen until the exposure dose is more than 20mg/kg[6]. Doses more than 40mg/kg induce seizures and life-threatening signs such as arrhythmias[6].

Cats may be more sensitive because of their low capacity of glucuronide formation. A cat developed bradycardia and ventricular extrasystoles (ventricular premature complexes) after ingesting a dose of 5mg/kg[6]. In humans, ingestion of LTG higher than 15g can be fatal[8].

Toxic mechanism

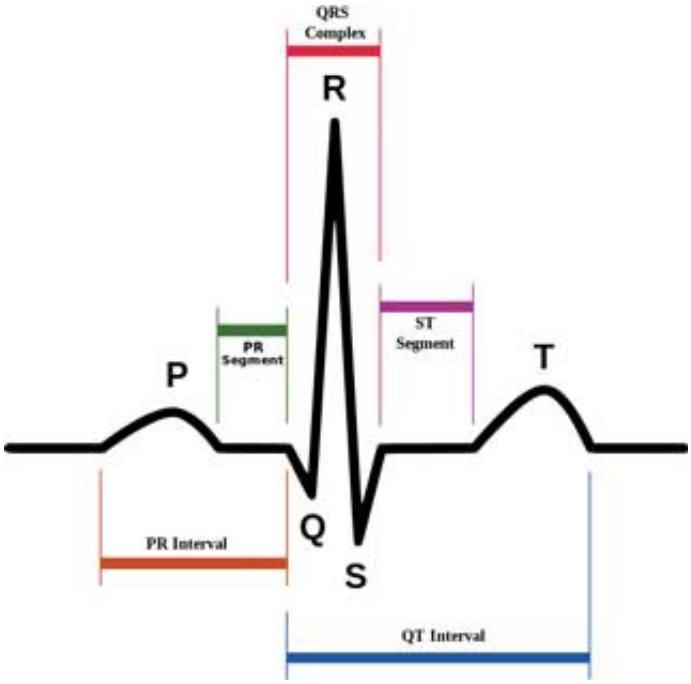

Figure 1. ECG showing cardiac conduction disturbances.

In dogs, LTG is extensively metabolised to a major metabolite cardiotoxic LTG-2-N-methyl[1].

In case of LTG poisoning, intraventricular conduction could be delayed resulting in prolonged electrocardiographic parameters: PR interval, QRS complex, QT interval (**Figure 1**). In acute poisoning, the effects of cardiac sodium channel blockade are consistent with widening of QRS complex[18]. Hypokalaemia induces prolongation of the PR interval. Potassium channel blockade results a prolonged QT interval[14,17]. Prolongation of the QT interval is associated with high risk for ventricular arrhythmias, torsade de pointes and sudden death. Treatment with phenytoin or phenobarbital, which inhibit hERG potassium channels and induce QT prolongation, contribute to the increased risk of ventricular arrhythymias[19].

Clinical features

Clinical signs of toxicosis most commonly occur within four hours after exposure and are delayed up to 12 hours with the extended-release products[5,6]. The common reported clinical signs include[5,6,18,20,21]:

- vomiting
- ataxia
- somnolence, lethargy
- tachycardia
- tremors, seizures which precede severe cardiac toxicity
- arrhythmias
- bradycardia
- hypersalivation

An ECG (**Figure 1**) shows cardiac conduction disturbances:

- PR interval prolongation first degree atrioventricular (AV) block (normal values PR interval – dogs 0.06sec to 0.13sec, cats 0.05sec to 0.09sec);
- widening of the QRS complex (normal values QRS duration – large dogs ? 0.06sec, small dogs ? 0.05sec, cats ? 0.04sec);
- prolonged QT interval (normal values – dogs 0.15sec to 0.25sec, cats 0.12sec to 0.18sec, depending on
  heart rate);
- various degrees of AV block.

Laboratory values indicate hypokalaemia, hypomagnesaemia and metabolic acidosis[6,8]. Death is due to cardiac arrhythmia.

Diagnosis

The diagnosis of LTG intoxication is based on the history of exposure, rapid onset of significant clinical signs such as CNS depression, seizures and cardiac disturbances. Toxicological diagnosis is based on analysis of vomits, blood, urine and saliva. Kidneys and liver can also be used to verify the presence of LTG in tissue collected postmortem.

The presence of LTG can be confirmed by various analytical methods: gas chromatography-mass spectrometry (GC/MS), liquid chromatography-mass spectrometry (LC/MS), liquid chromatography-tandem mass spectrometry (LC/MS/MS), homogenous enzyme immunoassay[9,11,22,23].

Management

There is no specific antidote. Management of LTG poisoning is listed in **Table 1**[1,6,24-29]. In human medicine, intravenous lipid emulsion is a potential antidote for the treatment of acute poisoning by

lipophilic cardiotoxic drugs that did not respond to standard therapies. The dosage recommended for dogs and cats is adapted from human literature.

Table 1. Management of LTG poisoning
Treatment to avoid
Gastrointestinal decontamination is not indicated (rapid absorption of LTG).
Vomiting is not recommended (potential for seizures of LTG).
Activated charcoal per os is contraindicated in an animal that is convulsing.
Urinary alkalinisation is not recommended.
Haemodialysis is not effective of removing LTG from the blood.
Phenytoin and phenobarbital are contraindicated.
LTG-induced QRS interval prolongation is refractory to the treatment with IV sodium bicarbonate.
Cats are very sensitive to lidocaine.
Amiodarone (antiarrhythmic) is contraindicated in dogs (may worse conduction disturbances).
Treatment to administer
Attention to airway, breathing and circulation are paramount.
One oral dose of activated charcoal (2g/kg to 5g/kg) mixed with water to make a slurry via nasogastric tube, after the airway is secured as soon as possible post-ingestion.
Antiemetics may be required (maropitant citrate injectable).
Seizures are managed with benzodiazepines: – diazepam IV bolus (0.5mg/kg to 2mg/kg). Repeat is necessary within 20 minutes (serum half-life in dogs: 2.5 hours to 3.2 hours) up to three times in a 24-hour period; or – lorazepam, a long-acting benzodiazepine, IV bolus (0.2mg/kg).
For bradycardia, administer IV atropine (0.022mg/kg to 0.044mg/kg).
Treat torsade de pointes with magnesium sulfate (30mg/kg IV slowly).
Correct hypokalaemia (serum concentration <3mEq/L) with IV potassium chloride through a central vein (not be infused at a rate greater than 0.5mEq/kg/hour).
Continuous ECG monitoring until normalisation.
Acidosis should be corrected.
Stable ventricular arrhythmias: lidocaine (antiarrhythmic) IV slowly (2mg/kg to 8mg/kg), then following by a constant rate infusion (CRI) of 0.025mg/kg/min to 0.075mg/kg/min, starting at a high dose and tapering down when possible, in dogs.
For rapid conversion of life-threatening, unstable ventricular arrhythmias: initial IV bolus lidocaine (1mg/kg to 2mg/kg over 30 seconds), then CRI at 0.025mg/kg/min to 0.080mg/kg/min in dogs.
Administer intravenous lipid emulsion (ILE) 20%: 1.5ml/kg IV bolus over one minute followed by a constant rate infusion of 0.25ml/kg/min for the next 30 minutes to 60 minutes. In patients that are non-responsive, additional intermittent bolus can be given IV slowly at up to 7ml/kg[37]. If clinical signs do not improve after 24 hours, discontinue ILE.

Table 1. Management of LTG poisoning

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