

Lamotrigine Monograph

Daniel G. Morrow, Pharm.D. candidate
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Lamotrigine (LTG) is an anticonvulsant medication approved for adjunctive antiepileptic therapy in adult patients with partial seizures. LTG is also approved for adjunctive use in Lennox-Gastaut generalized seizures in adults and children.¹ In January of 2002 the FDA approved LTG for adjunctive use in partial seizures in pediatric patients aged 2 years or older.² LTG is approved for monotherapy in adult patients converted from monotherapy with other enzyme-inducing antiepileptic drugs (EIAEDs) including carbamazepine (CBZ), phenobarbital, primidone and phenytoin.¹ Although FDA approval is limited to these indications, LTG has been used experimentally in virtually all types of epilepsy including absence and reflex seizures, status epilepticus, and epilepsy refractory to other medications.³ Other reported off-label uses of LTG include bipolar disorder, migraine headache with aura, and various pain syndromes including trigeminal neuralgia, neuropathy, and pain associated with multiple sclerosis.³

LTG is marketed under the brand name Lamictal® by Glaxo-Wellcome (a.k.a. GlaxoSmithKline) in the U.S., Australia, Belgium, Brazil, Canada, Denmark, France, Germany, Hong Kong, Ireland, Israel, Italy, Mexico, The Netherlands, Norway, New Zealand, Portugal, Singapore, Thailand, Austria, Finland, Sweden, Spain, Switzerland and the United Kingdom. Glaxo-Wellcome also markets LTG under the brand name Lamicitin® in South Africa. Additional LTG products include the brand name Neurium (DI)® produced by Sintofarma, Brazil and Labileno® manufactured in Spain by Faes.⁴

Lamictal® is available in 25, 100, 150 and 200 mg oral tablets and 2, 5, and 25 mg chewable, dispersible tablets. Each tablet contains the indicated amount of the active ingredient 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine (C₉H₇N₅Cl₂, MW=256.09).¹

The exact mechanism of LTG's anticonvulsant action is not completely understood. A pre-synaptic action on neuronal voltage-sensitive sodium channels leading

to membrane stabilization and inhibition of excitatory amino acid release is postulated as the most likely mechanism.^{1,5} In addition, LTG shows similar activity to other antiepileptic drugs (AEDs) such as CBZ and phenytoin by blocking the sustained firing of spinal cord neurons and delaying sodium channel recovery in mice.⁵ LTG is also acts as an inhibitor of dihydrofolate reductase leading to decreased folate synthesis. This can potentially lead to significant drug interactions if other folate inhibiting drugs are co-administered. LTG has demonstrated melanin binding in rodent tissue. A minor 2-N-methyl metabolic product of LTG metabolism is known to cause prolongation of the PR interval, QRS complex widening and AV conduction block at high doses in rodents.¹

Adjunctive dosing regimens for LTG vary according to the nature of concomitant antiepileptic medications. For patients 2-12 years old currently treated with an AED regimen that includes valproic acid (VPA), an agent known to inhibit LTG metabolism, an initial dose of 0.15 mg/kg/day for the first 2 weeks is recommended. An increase to 0.3 mg/kg/day in weeks 3-4 followed by a maintenance dose of 1-5 mg/kg/day with a maximum daily dose of 200 mg is recommended thereafter. Titration to the maintenance dose should be accomplished by calculating 0.3 mg/kg/day and rounding down to the nearest tablet. This dose should then be added to the previous daily dose with escalations attempted every 1-2 weeks. Dosing in these patients may be accomplished by giving a single or 2 divided daily doses. Dosing in patients 2-12 years old on EIAEDs who are not taking VPA should be started on 0.6 mg/kg/day in 2 divided doses for the first 2 weeks with an increase to 1.2 mg/kg/day in weeks 3-4. The usual maintenance dose for these patients is between 5 and 15 mg/kg/day with a maximum of 400 mg/day in 2 divided doses. To reach the maintenance dose a calculation of 1.2 mg/kg/day should be rounded down to the nearest tablet and added to the previously administered dose with increases every 1-2 weeks. When using weight-based dosing all doses should be rounded down to the nearest tablet and only whole tablets should be administered.¹ Adding LTG to an antiepileptic regimen that contains VPA in patients over 12 years old may be accomplished by giving 25 mg every other day in weeks 1-2 followed by 25 mg every day in weeks 3-4. The usual maintenance dose in these patients is 100-400 mg/day in 1 or 2 divided doses. Dosing may be increased by 25-50 mg/day every 1-2 weeks in order to reach the usual maintenance dose. Adjunctive dosing for patients older than 12 years who

are on EIAEDs without VPA should be initiated at 50 mg/day in weeks 1-2 followed by an increase to 100 mg/day in 2 divided doses in weeks 3-4. Usual maintenance dose in this group is 300-500 mg/day in 2 divided doses. Doses may be increased by 100 mg/day every 1-2 weeks in order to reach maintenance. When adding LTG to other antiepileptic regimens the manufacturer presents no specific guidelines. Conservative dosing (as in the case of adding to VPA) is recommended.¹

When converting from a single EIAED to LTG monotherapy in patients 16 years or older the LTG doses should be titrated to a maintenance dose of 500 mg/day using the same protocol as when adding LTG to an EIAED regimen that does not include VPA. During the dose escalation the EIAED should be maintained at a fixed level until the LTG maintenance dose is achieved and then gradually withdrawn. Decreasing the EIAED dose by 20% weekly over a 4-week period is recommended.¹

Although the manufacturer presents no specific modification of the dosing regimen for elderly patients, it does recommend a reduction of dose in hepatic impairment. In patients with Child-Pugh Grade B liver dysfunction a dose reduction of 50% is recommended for initial, escalation, and maintenance doses. A reduction of 75% is recommended for Grade C impairment. In addition, a reduction in dosage may be warranted in renal impairment although data concerning renal excretion in the elderly is limited.¹ Given these criteria, careful dosing in the elderly is warranted due to decreasing hepatic and renal function with advanced age.

Absorption of orally administered LTG results in peak plasma concentrations at 1.4-4.8 hours.¹ There is some evidence that enterohepatic recycling may lead to a second peak at 4-6 hours.³ Absolute bioavailability is reported as 98% with a volume of distribution of 0.9-1.3 L/kg. Plasma protein binding of LTG is reported as 55%. There appears to be little displacement of CBZ, phenytoin or phenobarbital from protein binding sites. 94% of an orally administered dose of LTG is eliminated in the urine and 2% in the feces. Glucuronidation is the primary means of LTG metabolism with 2-N-glucuronide, an inactive metabolite, accounting for 76% of the conjugated products detectable in the urine. Other detectable metabolites include 5-N glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified products that are believed to be

pharmacologically inactive. Unchanged LTG accounts for 10% of the products detectable in urine.¹

The rate of LTG clearance is increased by EIAEDs resulting in an elimination $t_{1/2}$ of 14.4 hours for single and 12.6 hours in multiple dose LTG therapy. VPA is known to decrease LTG clearance with a $t_{1/2}$ of 58.8 hours reported for adults taking VPA only. The LTG $t_{1/2}$ in adult patients taking EIAEDs and VPA is reported as 27.2 hours. For children aged 10 months to 5.3 years the LTG $t_{1/2}$ for patients on EIAEDs is reported as 7.7 hours, those on VPA only 44.9 hours, and those on other AEDs without known enzyme induction 19.0 hours. In patients 5-11 years old the LTG $t_{1/2}$ is 7.0 hours for those on EIAEDs, 19.1 hours for those on EIAEDs plus VPA, and 65.8 hours for those on VPA only. In healthy volunteers with no other concomitant medications the elimination $t_{1/2}$ for patients taking a single dose of LTG was reported as 32.8 hours vs. 25.4 hours in patients taking multiple doses. This finding has led to speculation that LTG may induce its own metabolism.¹

The most common adverse reactions associated with therapeutic dosing of LTG in adults include dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting and rash.¹ In rare instances LTG has been associated with anticonvulsant hypersensitivity syndrome (AHS), a severe complication also known to be related to use of CBZ, phenytoin, primidone and phenobarbital. The syndrome typically manifests as a fever that develops 2-6 weeks following initiation of therapy and can progress to a skin eruption, lymphadenopathy, hepatitis, eosinophilia, blood dyscrasias and nephritis.⁶ Less severe rash is also associated with LTG. An observational cohort study monitoring patients over 6 months identified rash as the most frequent reason for cessation of LTG therapy with 4.5% of patients reporting and a median time to onset of 41 days (95% CI 33-50 days). This study reported a higher incidence of rash in children aged 2-12 years than in adults.⁷ The incidence of rash with LTG, which is occasionally associated with Stevens-Johnson syndrome, AHS, and toxic epidermal necrolysis, has led to a “black box” warning from the manufacturer stressing the importance of adhering to the recommended initial dosing and escalation guidelines. Due to the unpredictable nature of rash associated with LTG, discontinuation of therapy is recommended at the first sign of rash.¹

No specific contraindications to LTG are suggested other than hypersensitivity to the drug or any of its components.¹

LTG is classified as an FDA pregnancy category C medication. Animal studies have not demonstrated teratogenicity. LTGs potential for inhibiting folate synthesis in humans indicates a potential for teratogenic effects that have not been studied.¹ Studies concerning placental transfer of LTG to the fetus and late-term effects are lacking.

Experience with LTG toxicity is limited and definitive studies examining the incidence of poisoning with this agent have not been conducted. One fatality was reported to the Toxic Exposure Surveillance System in 1999 involving a 10 year old male with a history of autism and seizures who presented in status epilepticus following an LTG dose increase.⁸ Therapeutic plasma concentrations for LTG have not been determined by the manufacturer, however they typically range from 1-4 µg/mL.⁹ One case report details a 32 year old woman who survived a peak LTG concentration of 35.8 µg/mL at 5 hours post-ingestion.¹⁰ The lethal dose of LTG has not been established however adults have survived ingesting doses over 4000 mg with treatment.¹⁰ One case of a 2 year old surviving an 800 mg overdose is documented.¹² Doses of up to 15 g have been suggested to be fatal.¹¹

Symptoms of CNS depression including, ataxia, somnolence, nystagmus and coma are associated with acute LTG toxicity.¹¹ Although the exact mechanism by which LTG induces these symptoms is not defined, such manifestations are consistent with an enhancement of LTG's proposed therapeutic mechanism of action. Generalized, tonic-clonic seizure has been reported in one case of a 2-year-old male with no history of epilepsy who ingested 800 mg of LTG.¹² An LTG level taken at 2 hours post ingestion revealed a plasma concentration of 3.8 µg/mL. Seizure is not reported in other adult cases of LTG toxicity and it is unknown whether this is a presentation characteristic of pediatric toxicity or the result of a proconvulsant effect. This patient presented with pronounced ataxia, hypertonia, and lack of motor coordination and muscle weakness however no nystagmus was observed. The child received gastric lavage, activated charcoal, and fluid replacement. Following admission to the PICU and observation for 48 hours he was released without further complications.¹² Hypertonia and ataxia were also observed in a 26-year-old male with a history of temporal lobe epilepsy who

intentionally ingested 1350 mg of LTG. Levels of 17.4 µg/mL and 6.4 µg/mL were reported at 3 and 17 hours post ingestion respectively. QRS widening (112 ms) was observed in this patient and it is postulated that this may be a voltage-sensitive channel effect similar to tricyclic antidepressant, phenytoin, and CBZ toxicity. This patient was hypokalemic upon presentation with a level of 3.3 mmol/L however no cardiac dysrhythmias developed. His QRS width was measured 2 months following discharge and was reported to be normal (<100 ms). This patient also received gastric lavage and activated charcoal and was released without known sequelae.¹³ A 32-year-old woman who ingested 4500 mg LTG and 2 mg clonazepam with alcohol also presented with ataxia and hypertonia. An LTG level of 35.8 µg/mL was reported 5 hours post ingestion and no ECG abnormalities were noted. Rotational nystagmus developed on the day following admission. Her symptoms gradually improved over the course of 48 hours and she was discharged 3 days after admission.¹⁰ An unusual presentation of LTG overdose involves the case of a 49-year-old male with bipolar disorder who unintentionally ingested 2700 mg of LTG daily for 4 days. This patient presented with AHS (low-grade fever [37.8°C], an erythematous, maculopapular rash on the face, trunk, and extremities and periorbital edema). Neurologic examination revealed no CNS abnormalities. LFT's were elevated (AST 154 IU/L and ALT 76 IU/L) and renal function was impaired (BUN 31 mg/dL and serum creatinine 2.4 mg/dL [baseline for this patient was 1.0 mg/dL]). Serum electrolytes were normal and white blood count was elevated ($19.1 \times 10^3/\text{mm}^3$). Successful treatment with a 4-week course of LTG (500 mg/day) 6 months prior to admission suggest that this was most likely not a typical hypersensitivity reaction. The patient was admitted and treated with prednisone. Over a 4-day course the symptoms and serum abnormalities resolved and the patient was discharged 6 days after admission. No long-term adverse effects of the overdose were reported.¹⁴

A quantitative HPLC assay for serum LTG levels is available, although interpretation of levels is limited due to lack of data relating serum concentration to toxicity. Serum levels that are within the typically observed therapeutic range (1-4 µg/mL) could be assumed to be safe for adults although symptoms have been observed to resolve at higher levels in both children and adults.^{10,12} Due to multi-organ involvement in AHS and the potential for hepatic and renal toxicity, monitoring of LFTs, serum

creatinine, and BUN is recommended in LTG toxicity. Electrolyte monitoring should also be performed with special attention paid to potassium levels due to a report of hypokalemia associated with LTG toxicity.¹³ Complete blood counts should be obtained to screen for leukopenia, thrombocytopenia and other hematologic complications. Without a clear understanding of the potential cardiotoxic effects of LTG overdose ECG monitoring should be instituted in order to detect QRS widening and PR prolongation.¹¹

Given the potential for significant CNS depression with LTG overdose and the subsequent risk of aspiration, syrup of ipecac administration is not recommended. Seizure resulting from LTG toxicity or underlying epilepsy is a further contraindication to emesis induction. Gastric lavage was performed on 2 of the 4 cases previously described although its effect on preventing further absorption is unknown.^{12,13} Therapeutic peak concentrations are typically reached between 1-5 hours after dosing, however the time to peak concentration in toxicity is unknown, whether lavage was beneficial in this case is undetermined. Use of activated charcoal is reported and recommended although its efficacy is unknown.¹¹ With some indication that LTG may undergo enterohepatic recycling, multiple dose activated charcoal may be of benefit, although there is no direct evidence of this.^{3,13} Data concerning the use of whole bowel irrigation in LTG overdose was not presented in any of the studies examined.

Most of the cases examined typically presented with good oxygen saturation and respiratory rates.^{10,12,13,14} The fatality reported in 1999 presented in status epilepticus and was intubated.⁸ Ventilatory support may be required in extreme cases of seizure or CNS depression. Potassium supplementation is indicated if hypokalemia develops in order to prevent arrhythmia. It is crucial to bear in mind that the majority of patients prescribed LTG have underlying epilepsy and may develop seizures as LTG or other concomitant AED drug levels are reduced by intervention. Treatment with benzodiazepines (diazepam or lorazepam) is recommended with progression to phenobarbital or finally phenytoin if these agents prove ineffective.¹¹ Rhabdomyolysis is a potentially fatal complication of prolonged seizure activity and should be aggressively treated with fluid replacement even if evidence of dehydration is absent.¹¹ Osmotic diuresis (mannitol) may also be indicated in cases where rhabdomyolysis, cerebral edema, or myoglobinuria develop.¹¹

Elimination enhancement through hemodialysis at toxic levels has not been studied although limited data suggests a 17-20% removal of drug over 4 hours in patients with renal failure on dialysis.^{1,11} Increasing the rate of elimination was not attempted in any of the examined cases and there is speculation that LTG may induce its own metabolism as previously described.¹¹ Elimination $t_{1/2}$ during a toxic episode was calculated as 19.5 hours in one adult female patient and 10 hours in one adult male.^{10,13} In the pediatric poisoning case report the $t_{1/2}$ was calculated as 13.5 hours.¹² These numbers generally fall within the reported timeframes documented by the manufacturer although concomitant medication effects on LTGs metabolism must be taken into account when estimating clearance.

There is no known antidote to LTG poisoning and care is generally supportive with observation following lavage and activated charcoal. Without quantitative studies to examine toxic and lethal LTG doses and plasma concentrations, history and clinical presentation are currently the only means of assessing patient risk. Most of the patients in the case reports examined resolved within 3-6 days with no permanent adverse effects from even large ingestions of LTG.

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