Clinical Medicine: Therapeutics

REVIEW

Safety and Efficacy of Lamotrigine in Older Adults with Epilepsy and Co-Morbid Depressive Symptoms

Yitzhak Schiller[1,3] and Norberto Krivoy[2,3]

[1]Department of Neurology and [2]Clinical Pharmacology Institute, Rambam Health Care Campus, and [3]B. Rappaport Faculty of Medicine, Technion, Haifa, Israel. Email: n_krivoy@rambam.health.gov.il

Abstract: Lamotrigine is an oral well absorbed antiepileptic medication (AED) from the phenyltriazine class approved by the FDA in 1994 for the treatment of epilepsy and in 2003 for the treatment of bipolar disorder. For epilepsy it is used to treat partial seizures, primary and secondary tonic–clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Lamotrigine is the only AED that treats the depressive as well as the maniac phases of bipolar disorders. It is important to consider lamotrigine adverse reactions and drug-drug interactions such as with other AED's, psychiatric medications, estrogens, and complementary-alternative medicines. Lamotrigine induces skin reactions as part of the hypersensitivity response (HSR), the actual incidence of skin rash is low (1.8%) providing slow escalation regimens are used when introducing this medication. An especially appealing indication for lamotrigine treatment is elderly epilepsy with depression. The main advantage of lamotrigine for the treatment of this indication in the elderly lies in its favorable and predictive adverse event profile and drug-drug interactions in comparison to other AEDs. Lamotrigine can serve in the elderly as both an antiepileptic and an antidepressant drug with a relatively favorable profile.

Keywords: lamotrigine, elderly, epilepsy, bipolar disorders

Clinical Medicine: Therapeutics 2009:1 825–833

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Epilepsy in the Elderly

In the year 2050, approximately 22% of the total world population is expected to consist of elderly individuals.[1] The incidence of new onset epilepsy increases in the elderly population, mostly due to epilepsy secondary to cerebro-vascular accidents (CVAs). The prevalence of epilepsy reaches approximately 3% at the age of 75 years.[2] Moreover, 9% of individuals admitted to old age homes in the USA suffer from epilepsy.[3,4]

Antiepileptic drugs (AED) are the treatment of choice for epilepsy. The goal of AED treatment is to prevent initiation of the epileptic seizures. Generally, AEDs are divided into "old" and "new". Old AEDs include carbamazepine, valproic acid, phenytoin and phenobarbital. New AEDs include, among others, gabapentin, lamotrigine, topiramate and levetiracetam. Treatment of epilepsy in the elderly population presents a special challenge to the treating physicians for several reasons: 1) the impact of seizures is greater in the elderly population, especially due to greater risks of trauma and fractures, and protracted post-ictal confusion, 2) adverse events of AEDs are enhanced in elderly patients, 3) other diseases that may worsen epileptic seizures or influence the pharmacokinetics of AEDs are more frequently found in elderly patients, 4) elderly patients tend to consume multiple other drugs that may interact with AEDs. According to recent publications, the therapy of elderly people suffering from epilepsy is mainly based on a single agent prescription. Moreover, recent studies have shown that new generation AEDs, especially lamotrigine, are superior to old generation AEDs in the treatment of elderly patients with epilepsy.[5,6]

Lamotrigine

Pharmacology[7–9]

Lamotrigine [3,5 diamino-6-2,3-dichlorophenyl)-1,2,4-triazine] is an antiepileptic medication (AED) from the phenyltriazine class approved by the FDA in 1994 for the treatment of epilepsy and in 2003 for the treatment of bipolar disorder. For epilepsy it is used to treat partial seizures, primary and secondary tonic–clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Lamotrigine is the only AED that treats the depressive as well as the manic phases of bipolar disorders, and it is the first medication since lithium to be granted FDA approval for the maintenance treatment of bipolar disorders. Off-label use includes the treatment of peripheral neuropathy, trigeminal neuralgia, cluster headaches, and migraines, and for reducing neuropathic pain and post-traumatic stress disorder.

Mechanism of action

The exact mechanism of action of lamotrigine has not been fully elucidated. It is thought to act by reducing the excitability of individual neurons and inhibiting the release of glutamate, an excitatory neurotransmitter, via inhibition of voltage-sensitive sodium channels.[10–15] While it does not block or reduce the rate of development of kindling, it does decrease the number of kindled responses and the duration of kindled seizures.[16] Further evidence that lamotrigine inhibits glutamate release is exhibited in the rat model, in which kainic acid neurotoxicity, mediated by glutamate release, is inhibited, while quinolinic acid and ibotenic acid neurotoxicity, mediated by N-methyl-D-aspartate (NMDA) receptor excitation, is not.[17]

Pharmacokinetic and metabolic profile

Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract. The time to peak drug concentration varies from 1.4 to 4.8 hours.[18] A second peak was reported at 4 to 6 hours, possibly due to enterohepatic re-circulation.[19] The therapeutic drug concentration is reported to be 1–4 mcg/ml.[4] Lamotrigine is approximately 55%–56% bound to plasma proteins, has a volume of distribution of 0.9–1.3 liter/kg,[20] with a mean area under the concentration-time curve (AUC) of 56.6 mg ∗ hour/liter in young adults. In the elderly, the AUC is increased by 55%.[20]

Its bioavailability was established to be 98%[21] and food does not affect the drug absorption from the gastrointestinal tract. The drug is extensively metabolized by conjugation with glucuronic acid. The known inactive metabolites are the 2-N and 5-N glucuronide conjugate, and the 2-N methyl metabolite is also inactive. The total body clearance of lamotrigine ranges between 0.2 to 1.2 ml/min/kg in adults.[18] The drug is 94% renal excreted, reduced in patients with renal failure.[20,23] Lamotrigine elimination half-life is 13–30 hours.[21,22]

The pharmacokinetic profile appears to be linear, and kinetic parameters after multiple dosing are similar to those observed after a single dose. Because

of the wide variability in lamotrigine kinetics caused by interaction with concomitant medications, monitoring serum lamotrigine concentrations could be theoretically useful in clinical practice.[22]

Seizure control can be reached by a lamotrigine concentration of 1–4 mcg/ml that remains to be confirmed.[10,19] Many patients have required higher levels.[19] In smokers, it has been demonstrated that smoking reduces lamotrigine blood concentration.[23]

The medication is a substrate for UGT and can auto-regulate this enzyme by inducing its synthesis.[24] The use of concomitant enzyme inducers decreases the half-life of lamotrigine from 29 to 15 hours. Of note is the interaction between lamotrigine and valproate. Since these two drugs compete for glucoronidation, lamotrigine metabolism will be inhibited, and the half-life increased to up to 59 hours. A second dose of lamotrigine in the presence of valproate will result in a further increase in blood lamotrigine concentrations and thereby potentiate its toxicity.[25,26] Indeed, higher incidences of idiosyncratic reactions were observed in patients in whom valproic acid was administered with high doses of lamotrigine.[27,28]

Lamotrigine clinical studies for epilepsy therapy

Lamotrigine is a broad spectrum AED that has been shown to effectively prevent epileptic seizures in partial and generalized epilepsy, and to work both as an add-on treatment for intractable (drug-resistant) epilepsy and as monotherapy for new onset epilepsy. Recently, lamotrigine has also been shown to be effective in treating bipolar disorder.

Like virtually all AEDs, lamotrigine was first shown to significantly prevent seizures in intractable partial epilepsy. Double-blind control studies showed that the addition of lamotrigine to the currently used AEDs was significantly more efficient than placebo in diminishing seizures in patients with intractable partial epilepsy.[29–36] In later studies, lamotrigine was shown to effectively treat new onset epilepsy as monotherapy.[37–40] Moreover, prior double-blind control studies have shown that lamotrigine has higher retention rates than old-generation AEDs, such as carbamazepine and phenytoin. This improved retention rate was caused by a significantly improved side-effect profile. For example, in the study by Brodie et al,[41] 65% of patients with new onset epilepsy treated with lamotrigine completed the 48-week trial, compared to only 51% of patients treated with carbamazepine. The difference in compliance between lamotrigine and carbamazepine was attributed to the difference in adverse events that resulted in discontinuation of carbamazepine. The improved retention rate of lamotrigine compared to old-generation AEDs was even more pronounced in elderly patients.[42–44] For example, in a targeted double-blind study performed in elderly patients (average age of 77 years) 71% remained on lamotrigine treatment for the entire 24-week trial period compared to only 42% of patients who remained on carbamazepine treatment during the entire 24-week trial period. Again the higher drop-off rate was caused by the better adverse event profile of lamotrigine.[37]

In addition to partial epilepsy, lamotrigine has also been shown to prevent generalized tonic-clonic seizures in primary generalized epilepsy.[45–47] Additional un-blinded studies have reported the beneficial effect of lamotrigine on other seizure types in generalized epilepsy, including myoclonic jerks and absence seizures.[48,49] Lamotrigine has also been shown to improve patients with the malignant epilepsy syndrome of Lennox-Gastaut.[50]

Lamotrigine clinical studies for bipolar disorder therapy and other affective disorders

Like most AEDs, lamotrigine has been shown to be effective for other non-epileptic indications. Double-blind controlled studies have shown that chronic maintenance treatment with lamotrigine significantly reduces relapses of both depression and manic episodes.[51–58] Lamotrigine was more effective in the prevention of depression, while lithium was more effective in preventing manic episodes.[52,54,57] In most studies, the efficacy of lamotrigine was proven during monotherapy. However, a recent study has also shown the efficacy of lamotrigine in bipolar disorder as an add-on treatment to lithium.[59] In addition to the adventitious effect of lamotrigine in bipolar disorder, lamotrigine has been suggested as augmentation therapy for severe treatment-resistant depression. In this case, lamotrigne is added to conventional antidepressants. Despite some positive studies that examined the effect of adjunctive lamotrigine therapy in treatment-resistant depression, the efficacy of

this treatment strategy has not yet been proven in well-controlled studies.[60–64]

Lamotrigine clinical studies for co-morbidity of epilepsy and affective disorders

Depression is a common co-morbidity in epilepsy patients.[65–68] This is especially true in the elderly.[69,70] An appealing possibility concerning lamotrigine is that it can be used to treat both epilepsy and depression in patients who suffer from both conditions. Few clinical trials have directly examined this possibility. These studies have shown that lamotrigine retains its anti-depressive efficacy in patients with epilepsy both generalized epilepsy and partial epilepsy.[71,72] The possibility to treat patients suffering form both epilepsy and depression with lamotrigine is especially appealing in elderly patients, due to the favorable adverse event profile of lamotrigine in this age group.[73,74]

Safety and adverse drug reactions

In a review from post-marketing surveillance (PMS) performed in refractory epilepsy, 12.4% of the patients treated with lamotrigine had stopped their therapy for reasons other than treatment failure.[75] Lamotrigine induces severe skin reactions as part of the hypersensitivity response (HSR) at a prevalence of 1/300 for adults and 1/100 for children.[76–78] The enhanced proliferation of peripheral blood mononuclear cells indicated T cell sensitization upon exposure to the drug. It has been suggested that this type of sensitization, either to the drug or a metabolite, might be involved in lamotrigine-induced hypersensitive syndrome.[28]

The actual incidence of skin rash with lamotrigine therapy is now low, providing slow escalation regimens are used when introducing this medication, occurring in only 1.8% of 10,894 treated individuals.[75]

The most dangerous reaction that lead to the withdrawal of lamotrigine was serious skin rashes, including Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[79–81]

Hypersensitive Reactions (HSRs) associated with lamotrigine may seem mechanistically different from those associated with the older AEDs, but they involve similar processes.[82] Nausea/vomiting, sedation/drowsiness, dizziness, headaches, malaise, visual defects, ataxia, aggression and depression were observed in less that 1% of exposed subjects.

In a study on 150 elderly suffering from epilepsy, Brodie et al[37] demonstrated that elderly subjects on carbamazepine developed 42% of adverse reactions in comparison to those on lamotrigine who developed only 18% of adverse drug reactions (ADR). In the same study, 39% of patients on lamotrigine were free from epileptic features after 16 weeks of participating in the study, in comparison to those on carbamazepine (21%).

In a 12-month study on 593 elderly receiving carbamazepine, lamotrigine or gabapentine, 44% of those on lamotrigine were withdrawn because of ADRs, while 51% and 64%, respectively, of those on gabapentine and carbamazepine were withdrawn for the same reasons.[83] An early study done by Maggs et al[84] provided *in vivo* evidence that lamotrigine can be oxidized when none of the other major competing pathways are saturated or blocked. Thus far, experiments in rats indicate the formation of an arene oxide from the O-dichlorophenol moiety of lamotrigine and that inhibition of the major metabolic pathway, N-glucuronidation, increases the risk of skin reactions.[82]

Very unusual adverse events have been described when using lamotrigine, such as: increased PR interval in an EKG and hypotension;[85] a few case reports about hyponatremia and weight gain;[86] some case reports about anemia and pancytopenia;[87] hepatitis, hyperbilirubinemia,[88] and one case report about liver failure.[89] Muscle pain and myolysis have been reported,[90] and anxiety, dysomnia and visual hallucinations have been described.[91]

The mechanism of bone disease-associated with antiepileptic medications has not been clearly elucidated. To date, there have been no reports of altered bone metabolism in individuals receiving the newer antiepileptics, such as lamotrigine.[92,93]

Lamotrigine interactions

Lamotrigine induces its own metabolism. The drug is a substrate for uridine diphosphate glucoronosyltransferase and can auto-regulate this enzyme by inducing its synthesis.[24]

Antiepileptic medications

Clearance of lamotrigine may double during concomitant therapy with *carbamazepine*.[94,95] While lamotrigine alone has a steady-state elimination

half-life of 25–37 hours, coadministration of carbamazepine reduces the half-life to approximately 14 or 15 hours.[96–98] Lamotrigine clearance ranged from 0.021–0.035 L/h/kg(0.35–0.59 mL/min/kg)inhealthy volunteers given lamotrigine alone.[99,100] Comparable values during combination therapy ranged from 0.044–0.084 L/h/kg (0.73–1.4 mL/min/kg).[97,101,102] Carbamazepine was found to incrementally decrease the half-life of lamotrigine by 1.7 hours for every 100 mg of carbamazepine within the dosing range of 800–1600 mg daily.[97]

The use of *oxcarbazepine* reduced lamotrigine concentrations with possible loss of seizure control. The concomitant use of lamotrigine with *phenytoin* will reduce lamotrigine blood level concentration and reduce lamotrigine therapeutic effect. Higher doses of lamotrigine are needed when given concurrently with enzyme-inducing drugs, such as *phenytoin* and *carbamazepine*. When given in combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial lamotrigine dose of 50 mg once daily for the first two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weeks, advancing by 100 mg daily every two weeks to a total daily dose of 300–500 mg administered in two divided doses.[96,98,103]

Valproic acid prescribed together with lamotrigine increased the elimination half-life of lamotrigine, leading to lamotrigine toxicity (fatigue, drowsiness, ataxia) and an increased risk of life-threatening rashes.[96,98]

Psychiatric medications[104–106]

Sertraline, risperidone and *escitalopram* are involved in drug-drug interactions with lamotrigine. Increased risperidone plasma concentrations and subsequent toxicity were reported in a patient receiving lamotrigine in addition to a stable dose-regimen of *risperidone* and *clozapine*. Prescription of sertraline will produce an increased risk of lamotrigine toxicity (fatigue, sedation, confusion, decreased cognition). Myoclonus occurred in patients receiving escitalopram and lamotrigine concomitantly, and symptoms resolved following withdrawal of escitalopram in one patient. There was no evidence of a metabolic enzyme interaction with lamotrigine, and the interaction was believed to be due to the additive/synergistic effect of lamotrigine and escitalopram on the 5-HT1A receptors, or by an additive inhibition of voltage-gated calcium channels by both agents. Caution should be exercised when using both drugs concurrently and signs and symptoms of myoclonus, including involuntary twitching and jerking, should be monitored.

Other medications

The therapeutic use of *acetaminophen* enhances the urinary elimination of lamotrigine after single doses of the anticonvulsant. In healthy volunteers, the administration of a single 300 mg dose of lamotrigine followed by acetaminophen 900 mg 3 times a day resulted in a decrease in AUC and serum half-life of 20% and 15%, respectively, compared to the administration of lamotrigine with placebo. No differences in peak plasma concentration or time to peak were observed. The percentage of lamotrigine recovered in the urine was also higher when administered with acetaminophen. It was suggested that acetaminophen may enhance removal of lamotrigine from the circulation.[107] The concomitant prescription of lamotrigine with *estrogens* will reduce or increase lamotrigine blood levels; this must be taken into consideration when fertile females are treated for epilepsy.[108]

Complementary alternative medicine

Evening primrose reduced anticonvulsant effectiveness. Theoretically, evening primrose oil may reduce the effectiveness of anticonvulsants by lowering the seizure threshold. Evening primrose oil is contraindicated in patients with epilepsy.[109,110]

Ginkgo decreased anticonvulsant effectiveness. The majority of ginkgo leaf products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly assayed to assure that 4'-O-methylpyridixone is not contained in the commercial product. Of concern are those instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (e.g. infants or those with known seizure disorders).[111]

Lamotrigine in liver failure

In patients suffering from chronic liver disease grades A, B and C (Child-Pugh), the median apparent volumes of distribution were 0.31; 0.24 and

0.1 ml/kg, respectively. Their median half-life was 36; 60 and 110 hours accordingly.[112] The manufacturer[18] recommends that the initial dose escalation and maintenance doses should be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites. In patients with severe hepatic impairment with ascites, the initial escalation and maintenance doses should be reduced by approximately 50%. Clinical response should also be considered during escalation and maintenance dosing. The present data point to the need for drug dose adjustment in chronic liver disease. It is recommended carrying out the dose adjustment under therapeutic drug monitoring (TDM) control.

Lamotrigine in renal failure and in hemodialysis

In patients with renal function impairment, a dose reduction is recommended;[113] while others have suggested that impaired renal function would have little effect on the plasma concentrations of lamotrigine for a given dosing regimen.[114] The total drug removed by hemodialysis during a 4 hour session is 17%–20% of the total body drug content. A supplemental dose is not recommended.[114] In patients suffering chronic renal failure, the mean half-life of lamotrigine given in a 100 mg dose was 43 hours while, in patients on hemodialysis, the mean half life was 13 hours during hemodialysis and 58 hours between sessions.[114] Thus, chronic renal failure patients under hemodialysis need drug dose adjustment under TDM control.

Place in Therapy

Lamotrigine is a broad-spectrum, new generation antiepileptic drug that is widely used in the treatment of patients with epilepsy and bipolar disorder. The main advantage of lamotrigine lies in its favorable and predictive adverse event profile in comparison to other, older, AEDs and some new generation AEDs, such as topiramate. In recent years, attention has been drawn to epilepsy in the elderly population. The incidence and prevalence of epilepsy increases with age due to symptomatic epilepsy secondary to cerebro-vascular and other neurological diseases. Moreover, the impact of seizures is greater in the elderly population especially due to trauma, fractures and prolonged post-ictal confusion. The advantage of lamotrigine as an effective broad spectrum AED with a favorable adverse event profile is even more pronounced in elderly patients. An especially appealing indication for lamotrigine treatment is elderly epilepsy patients with depression. In these patients, lamotrigine can serve as both an antiepileptic drug and an antidepressant drug with a relatively favorable adverse event profile.

Conclusions

The relatively favorable and predictable adverse event profile and the low drug-interaction potential of lamotrigine, together with the fact that the antiepileptic efficacy of lamotrigine as monotherapy is similar to that of other drugs, render lamotrigine as the antiepileptic treatment of choice for most elderly patients with epilepsy. Additional antiepileptic drugs and antidepressants should be considered in more severe epilepsy patients who are not fully controlled by lamotrigine monotherapy.

Disclosure

The authors report no conflicts of interest.

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