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REVIEW

Efficacy, safety, and potential of extended-release lamotrigine in the treatment of epileptic patients

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Abstract: Epilepsy is a frequent, chronic disease demanding long-term medication with antiepileptic drugs (AEDs). When slow release formulations of AEDs are used the chance of compliance and control of seizures is increased. Lamotrigine (LTG) is a broad spectrum antiepileptic drug (AED), effective against both generalized and partial seizures. Its immediate-release formulation (LTG-IR) requires twice-daily dosing. In contrast, an extended-release formulation (LTG-XR) may be given once daily, providing a flatter dose-concentration curve with apparently lower maximum serum levels. Simplified dosing positively affects compliance and LTG-XR has a similar profile of efficacy and tolerability to LTG-IR. Rashes, including Stevens–Johnson syndrome, are the most serious adverse effect impacting 0.8% of pediatric patients. Thus, LTG-XR should be discontinued upon the appearance of rash.

Keywords: epilepsy, antiepileptic drugs, extended-release, lamotrigine, adverse reactions, tolerability, pharmacokinetics

Introduction

Epilepsy is regarded as one of the most common neurological disorders affecting about 1% of the world's population.[1] There are about 20 to 70 new cases each year per 10,000 individuals. Interestingly, the lifetime chance of developing epilepsy is estimated from 3% to 5%.[1]

Epilepsy may be a consequence of genetic factors, brain tumors, trauma or infections, stroke, developmental disturbances (eg, cortical dysplasia), neurodegenerative diseases, malformations (eg, tuberous sclerosis, neurofibromatosis), or vascular malformations (eg, arteriovenosus malformations).[2] According to the classification of the International League Against Epilepsy (ILAE), seizures are either partial or generalized. A partial, or focal, seizure is evident when its initial semiology and electroencephalogram (EEG) manifestations are encountered in a specified brain region at the onset of a seizure. On the other hand, generalized seizures involve both cerebral hemispheres at the start of the convulsions.[2]

Management of epilepsy may be complicated by multiple epilepsy syndromes possessing varied pharmacosensitivities and, moreover, by inter-individual differences regarding disposition of antiepileptic drugs (AEDs).[3] In the past two decades, a considerable number of new AEDs have been introduced and presently there are more than 20 medications available. Consequently, there are many therapeutic options and antiepileptic therapy can be tailored according to the patient's individual circumstances. However, numerous options may also lead to choosing inappropriate or suboptimal AEDs. For most seizures, there is generally no significant difference in AED efficacy and therefore other factors chiefly

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influence the appropriate drug selection. These factors are related to the epilepsy syndrome, seizure types, potential side effects, comorbid conditions, concomitant medications, and the age and gender of the patient. The choice of a given AED or combination should be guided by knowledge and familiarity with AEDs and their interactions.[4] Some recommendations and guidelines (eg, American Academy of Neurology [AAN], European Medicines Agency [EMEA], National Institute for Health and Clinical Excellence [NICE], Scottish Intercollegiate Guidelines Network [SIGN]) exist for the proper use of AEDs.[5,6] For instance, AAN evidence-based guidelines recommend lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for adjunctive treatment of partial adult epilepsy and lamotrigine, gabapentine, topiramate, or oxcarbazepine for pediatric partial epilepsy.[5]

Pharmacology and pharmacokinetics of extended-release lamotrigine

Lamotrigine (LTG) is a broad spectrum AED that effectively protects in the form of add-on therapy against partial seizures, the generalized seizures of Lennox–Gastaut syndrome, and primary generalized tonic-clonic seizures in adults and children aged at least 2 years. This AED is also approved for conversion to monotherapy in adults.[7] LTG is available as an immediate-release formulation (LTG-IR) that undergoes a rapid and almost complete absorption following oral administration, with peak plasma levels being recorded from 1.3 to 4.7 h. The elimination half-life ($t_{1/2}$) after a single oral dose is above 30 h and multiple doses of LTG lead to a considerable reduction of about 24 h.[8] Glucuronidation in the liver by UGT1A4 is the main metabolic pathway for this AED[9–11] and it is clear that AEDs significantly affecting the activity of this enzyme may also distinctly modify pharmacokinetic parameters of LTG. For instance, carbamazepine (CBZ) and phenytoin (PHT) are strong inducers of UGT1A4 and their combined treatment with LTG results in a substantial increase in its systemic clearance.[12,13] Also, enzyme inducers (ie, CBZ, PHT) are responsible for the significant reduction in the LTG's elimination half-life from approximately 24 to 13 h.[12,13] In contrast, valproate (VPA) as an inhibitor of glucuronidation has been documented to significantly reduce the clearance of LTG with a concomitant increase in its elimination half-life from approximately 37 to 48 h.[14] Moreover, LTG serum concentrations were significantly increased from 4.67 ± 3.66 (LTG monotherapy) to 9.56 ± 5.27 μg/mL in patients receiving both, VPA and LTG.[15] In this context, the maintenance daily dose of LTG may differ, depending on whether a patient is taking enzyme inducers or VPA. Generally, most of the newer AEDs have no impact on the activity of hepatic enzymes so they are not expected to affect pharmacokinetic parameters of LTG.[16]

Importance of extended-release formulations

Extended-release formulations assume converting immediate-release drugs possessing short half-lives into drugs with pseudo-long half-lives. This procedure considerably reduces the number of daily doses to one or two. Moreover, almost constant drug serum concentrations may be maintained.[3] With IR formulations, the drug peak serum concentration may be associated with considerable adverse effects which can be avoided with XR drugs because the overall serum dose-concentration curve is flatter. Moreover, the flatter dose-concentration curve helps to avoid a drug trough level, which makes seizure control more efficient.[3] Lastly, XR formulations are associated with much better compliance as the dosing frequency is only one or two doses per day.[3]

Potential shortcomings of such formulations cannot be overlooked, however. For instance, a missed dose is more likely to provoke a seizure if an AED is prescribed once daily due to a rapid decline in AED serum concentration.[17] Therefore, better compliance may be actually complicated by missing a dose. This problem may be overcome by administering two doses a day for XR formulations approved for only once-daily dosing.[17] At present, there are XR formulations for CBZ,[3] PHT,[3] VPA,[3] and levetiracetam[18] and the United States Food and Drug Administration (FDA) has recently approved XR Lamotrigine (Lamictal® XR™; GlaxoSmithKline, London, UK) as a once-a-day add-on therapy for partial onset seizures with or without secondary generalization in patients aged at least 13 years.[19]

LTG-IR was initially introduced in the form of adjunctive therapy in adult partial epilepsies and subsequently in children above the age of 2 years, however, its efficacy has been shown down to one month of age.[3] During clinical trials in adults this AED was applied in daily dosages of 200–500 mg. Trough serum concentrations of only 1–4 μg/mL were observed since, in most cases, LTG was added to enzyme-inducing antiepileptic drugs (EIAEDs).[3] It is remarkable that even serum concentrations of 15 μg/mL are generally well tolerated.[3] LTG is also indicated against generalized seizures in Lennox–Gastaut syndrome and has been approved for conversion to monotherapy.[3] Interestingly, LTG has been

found to be effective in treating bipolar disorder and neuropathic pain syndromes.[3,20] More studies are necessary to evaluate its possible efficacy in the treatment of Alzheimer's disease and cocaine addiction.[20]

LTG-IR is recommended twice-daily in the form of monotherapy or add-on therapy with enzyme inducers. This dosing may be reduced to once-daily administration when LTG-IR is combined with VPA.[8] Logically, a formulation providing therapeutic drug serum concentrations, given once a day, can positively affect compliance. LTG-XR, due to a special eroding matrix, considerably reduces the rate of LTG release over 12–15 h.[3] An enteric coating additionally prevents LTG release which starts when a tablet passes to the duodenum.[17]

Pharmacokinetics of LTG-XR

In the Tompson et al Compass study,[7] the main outcome of enrolling the epileptic patients to LTG-XR once-daily dosing as an add-on LTG formulation resulted in a slower rate of absorption and reduced fluctuations in this AED serum concentration, when compared to LTG-IR administered twice a day. Steady-state concentration was achieved after two weeks of LTG-XR administration in patients who previously were given twice-daily LTG-IR for 14 days. The median time for the maximal serum concentration (T_{max}) following an oral dose of LTG-XR was, in the period of 15–28 treatment days, 4–6 h in the group receiving EIAEDs (induced group), 6–10 h in the group on neutral AEDs (neutral group), and 9–11 h in patients prescribed VPA (inhibited group). It is noteworthy that the median T_{max} for LTG-IR ranged from 1 to 1.5 h independently of the accompanying AEDs.[7] Dose-normalized steady-state serum maximal concentrations (C_{max}) of LTG were lower in patients on LTG-XR: 29% in the induced and 11% lower in the remaining two groups. On the other hand, steady-state LTG minimal concentrations (C_{min}) were comparable to those found in patients on LTG-IR. The mean fluctuation indices in patients receiving LTG-XR were approximately 27%–37% lower compared to the LTG-IR group.[7]

Efficacy and adverse effects of LTG-XR

Although the Compass study[7] was mainly devoted to the comparison of pharmacokinetic parameters of LTG-IR and LTG-XR, the authors also recorded adverse effects. The patients (a total of 44 and aged at least 13 years) enrolled in this study experienced partial seizures (55%), generalized seizures (23%) or both generalized and partial seizures (23%). The mean seizure frequencies per week did not differ significantly in three phases of this study (baseline phase, LTG-IR twice-daily for two weeks with concomitant AEDs; XR treatment phase, LTG-XR once-daily with the AEDs for two weeks; and IR phase, switching back to twice-daily LTG-IR for one week) and were 1.8, 1.4, and 1.5, respectively. The major adverse effect was headache which affected three out of 44 patients in the first phase (7%) and six out of 38 patients in the second phase (16%). No headaches were reported in the third phase of this study. Other adverse effects (eg, vomiting, insomnia, nausea, tremor) were not observed in more than 3% of patients.[7]

The Armor study[21] evaluated patients naïve to LTG, aged at least 13 years, and treated with one or two AEDs with an 8-week baseline phase. Those who experienced eight or more partial seizures were randomized to groups on either once-daily LTG-XR (118 patients) or placebo (121 patients), and both groups were taking the former antiepileptic treatment. The initial seven weeks corresponded to the escalation phase and the next 12 represented the maintenance phase. The total median reduction in the seizure frequency was 47% vs 24.5% for placebo with the respective results for the escalation and maintenance phases being 30% vs 16% and 58% vs 27%. Remarkably, 19% of patients (vs 5% for placebo) became seizure free during the maintenance phase and 44% vs 21% for placebo achieved at least a 50% reduction in their seizure frequency. As for the adverse effects, the most commonly reported were dizziness (19% vs 5% placebo), headache (16% vs 18%), somnolence (7% vs 4%), nausea (7% vs 2%), diarrhea (7% vs 4%), and nonserious rash (2% vs $<$1%). In no case was serious rash evident.[21]

Both studies cited above indicate that LTG-XR was effective against partial and generalized seizures with no serious adverse effects. Since the active substance of LTG-XR and LTG-IR is the same, there is no reason to assume that the efficacy of these formulations may differ. LTG has been documented to block voltage-dependent sodium channels and non-*N*-methyl-*D*-aspartate (NMDA) receptors along with inhibiting glutamate release, which probably determines its broad spectrum of activity.[22,23] LTG-IR has been found to be effective against generalized epilepsy syndromes in non-controlled designs.[3] This AED has also shown efficacy in the absence of childhood or juvenile myoclonic epilepsy.[3] However, myoclonus and myoclonic epilepsy in infancy may be worsened by the use of LTG-IR.[3] Since in many cases LTG is prescribed as an adjunctive AED, the final outcome of a drug combination may be dependent upon the second AED in the combination. In the case of LTG its interactions with

other AEDs yield all major types of interactions: synergy, additivity, and antagonism, both in terms of the anticonvulsant action and neurotoxicity. Preclinical data based upon the test of maximal electroshock in mice indicate that synergy was observed when LTG was combined with VPA, gabapentin, or topiramate.[24,25] Neurotoxicity was antagonistic for LTG + VPA and LTG + topiramate, pointing to the best preclinical profile of these combinations.[24] When LTG was co-administered with gabapentin, there was no neurotoxicity for a 50% anticonvulsant effect of this combination.[25] In contrast, an anticonvulsant antagonism was evident for the combined treatment of LTG + CBZ or oxcarbazepine, their respective neurotoxicities being additive and synergistic.[24,26] Evidently, the preclinical data suggest that combinations of LTG with CBZ or oxcarbazepine are to be avoided in clinical practice. There are also examples of additivity both in the convulsive and neurotoxic tests involving LTG + levetiracetam or retigabine.[27,28] All preclinical data were verified with brain concentrations of AEDs and in no case was a pharmacokinetic interaction shown.[24–28] The clinical reports are generally in line with the preclinical data. For instance, LTG monotherapy was found to be superior to LTG + CBZ in drug-refractory epilepsy[29] and LTG + VPA or topiramate was evidently synergistic in epileptic patients.[30] Preclinical data on interactions of LTG with other AEDs are summarized in Table 1.

Werz[3] reviewed the tolerability of LTG-IR and listed adverse effects which were found to be at least 3 percentage points higher in LTG-IR patients than in placebo patients and included: dizziness, diplopia , ataxia, nausea, blurred vision, somnolence, vomiting, abnormal coordination, tremor, insomnia, and rhinitis. Among these, ataxia, diplopia, dizziness, and nausea were statistically more frequently associated with LTG. Rash occurred in 10% of treatment patients versus 5% in the placebo group. However, cases of rash requiring hospitalization did not exceed 0.3% (the total of 3071 patients) and those with Stevens–Johnson syndrome represented 0.1%. The initial dose of LTG and the rate of titration seem critical for the occurrence of rash as a positive correlation has been observed. For instance, the initial dose of 25 mg was associated with a rash incidence of ca 1%; for 50 mg, the incidence was approximately 9%; 100 mg, approximately 12%; and 200 mg, approximately 38%. When the fifth week of titration was considered, LTG in the dose of 62.5 mg was associated with a 1.5% incidence of rash while that of 375 mg led to 12% rash incidence. A recommendation by the LTG manufacturer to reduce the initial titration rate considerably diminished the rash incidence, including serious cases. Noteworthy, due to this recommendation LTG-IR has proven, since 1993, to be comparable to other AEDs (CBZ, phenobarbital, PHT, or zonisamide) in terms of inducing rash problems. With regards to quality of life, approximately 30% of patients reported tiredness and cognition problems, however, LTG seems to affect the quality of life much less than other AEDs such as CBZ, PHT, topiramate, and VPA.[3]

Now, there are recent data available on the tolerability of LTG-XR (LAMICTAL® XR™).[31] In adjunctive therapy, this AED is associated with an incidence of rash in 0.3% of treated adults and 0.8%, including Stevens–Johnson syndrome, in pediatric patients (aged 2–16 years). In a group of 1983 pediatric patients treated with LTG-XR there was one death related to rash. Therefore, the drug should not be given to pediatric patients aged under 13 years. So far, the existing post-marketing experience has recorded isolated deaths related to toxic epidermal necrolysis or rash, but due to their low numbers the precise incidence rate is not known. Some unproven hypotheses exist that the risk of rash may be positively correlated with the combined treatment of LTG-XR with VPA and/or exceeding the recommended initial dose or dose escalation for LTG-XR. It is not practically possible to predict the evolution of rashes from benign to life-threatening which is why this AED needs to be discontinued immediately upon the appearance of rash. The only exception is if the rash is determined to be a nondrug-related episode.

Adverse effects of both immediate and extended-release LTG formulations are listed in Table 2. It can be seen that the XR formulation was considerably better tolerated. For instance, dizziness, diplopia, ataxia, and nausea were observed in 35% (vs 5% placebo), 25% (vs 6% placebo), 20% (vs 6% placebo), and 19% (vs 9% placebo) respectively of patients treated with LTG-IR. By contrast occurrence of

Table 1 Preclinical data on the interaction profile of lamotrigine (LTG) with conventional and newer antiepileptic drugs (AEDs) in electroconvulsions in mice

	CBZ[24]	GBP[25]	LEV[27]	OXC[26]	RET[28]	TPM[24]	VPA[24]
LTG	$\downarrow^{Add}$	$\uparrow$	0^{Add}	$\downarrow^{Syn}$	0^{Add}	$\uparrow^{Ant}$	$\uparrow^{Ant}$

Notes: All interactions in the seizure test were calculated by isobolography. Neurotoxicity was evaluated by an isobolographic analysis with the exception of LTG + GBP. In this case, neurotoxicity was estimated for the 50% anticonvulsant effect of the combined AEDs and there was no impairment of motor performance in the chimney test.
Abbreviations: CBZ, carbamazepine; GB, gabapentin; LEV, levetiracetam; OXC, oxcarbazepine; RET, retigabine; TPM, topiramate; VPA, valproate; $\uparrow$, synergy; 0 = addition; $\downarrow$ = antagonism in the seizure test; Syn, synergy; Add, addition; Ant, antagonism in the neurotoxicity test (chimney test).

Table 2 Adverse effects of lamotrigine immediate-release (LTG-IR) and lamotrigine extended-release (LTG-XR) formulations: Treatment vs placebo group (in %)

Adverse event	LTG-IR[3]	LTG-XR[31]
Dizzines	35 vs 5	19 vs 5
Diplopia	25 vs 6	4 vs 0
Ataxia	20 vs 6	5 vs 0
Nausea	19 vs 9	7 vs 2
Blurred vision	13 vs 4	4 vs 2
Somnolence	13 vs 7	7 vs 5
Rash	10 vs 5	2 vs 1
Vomiting	10 vs 5	4 vs 2
Insomnia	6 vs 3	≥2[a]
Tremor	5 vs 1	7 vs 2

Note: [a]denotes uncertain relationship to LTG-XR[31].

these adverse effects was noted in only 19% (vs 5% placebo), 4% (vs placebo), 5% (0 placebo), and 7% (vs 2% placebo) of patients administered LTG-XR.[3,31]

A very important question arises whether LTG may actually possess a teratogenic potential. Available data indicate that birth defect rates with LTG-IR are comparable to those of CBZ which are lower than previously assumed.[32] In this context, VPA bears the highest malformation potential which appears to be 2–3-fold greater than that of LTG or CBZ.[32] However, the use of LTG during pregnancy may be complicated by its changing pharmacokinetic properties resulting in lower serum concentrations which may eventually lead to breakthrough seizures.[32] This serious problem may be overcome with LTG dose adjustments, based upon monthly drug serum evaluations.[33] Strikingly, add-on LTG may lower the malformation risk from VPA[34] although contradictory views exist to suggest that this AED combination is particularly teratogenic.[35]

Dosage and administration

LTG-XR is recommended for once-daily use while escalation and maintenance doses are dependent on existing antiepileptic treatment.[31] The recommended initial and escalation doses must not be exceeded to prevent the possibility of a rash. In the case of conversion from LTG-IR to LTG-XR, the initial dose of the latter should match the total daily dose of the former. If, during conversion, patients take EIAEDs then the serum concentrations of LTG may be reduced and these patients usually require drug monitoring. When necessary, LTG dose adjustments should be applied.

Conclusions

Evidence indicates that treatment compliance is negatively correlated with the frequency of daily drug dosing. For instance, once-daily dosing is associated with 73%–87% compliance while that of twice-daily dosing is 70%–81%, three times daily is 52%–77%, and four times daily is 39%–42%.[5] LTG-XR may therefore be considered a formulation beneficial for increasing compliance, especially in patients with poor conformity to twice-daily LTG-IR.[36] This drug also provides a flatter drug-concentration curve which, by reducing the maximum LTG levels, is assumed to be better tolerated. The desired pharmacokinetic parameters for LTG-XR have been confirmed in the Compass study.[7] This study also provided evidence regarding the efficacy of LTG-XR against partial and generalized seizures and the overall tolerability of this AED. The authors are of opinion that switching directly from LTG-IR to LTG-XR requires the same total daily dose of LTG.[7] Another double-blind and placebo-controlled study has found LTG-XR to be effective against partial seizures with a good tolerability profile.[21]

Usually, little attention is paid as to which AED LTG is added to in the form of adjunctive therapy with regards to final protection against seizure activity. The presented preclinical data[24–28] along with clinical studies,[29,30] clearly indicate that combinations of LTG + CBZ or oxcarbazepine should be avoided.

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