Lamotrigine – An Update

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ABSTRACT: Lamotrigine (LTG) inhibits repetitive high frequency firing in depolarised neurones by selectively prolonging slow inactivation of the sodium channel, thereby suppressing the release of excitatory amino acids. It has been shown to be effective in 11 pivotal double-blind add-on trials in patients with refractory partial seizures with or without secondary generalisation. Subsequent anecdotal data support its efficacy for typical and atypical absences, myoclonic jerks, tonic or clonic seizures, Lennox-Gastaut syndrome and infantile spasms. Most recently LTG has been compared with carbamazepine and phenytoin in double-blind trials in patients with newly diagnosed partial and primary and secondary generalised tonic-clonic seizures. At the doses used, its efficacy was similar to the older agents for all seizure types, but LTG was better tolerated than both of the older agents. The commonest side-effects with LTG include headache, nausea, diplopia, dizziness, ataxia and tremor. Rash occurs in fewer than 5% patients. Its incidence can be reduced by starting treatment with a low dose, particularly in patients receiving concomitant sodium valproate which inhibits LTG metabolism. Enzyme inducers, such as carbamazepine, phenytoin and phenobarbital, accelerate its elimination, but LTG itself has no effect on hepatic metabolic processes. A pharmacodynamic interaction with carbamazepine necessitates a dosage reduction in some patients when LTG is introduced. LTG is a new antiepileptic agent with a long elimination half-life, a broad spectrum of activity, and a wide therapeutic ratio.

RÉSUMÉ: La lamotrigine - mise à jour. La lamotrigine (LTG) inhibe les décharges répétitives à haute fréquence des neurones dépolarisés en prolongeant sélectivement l'inactivation lente des canaux sodiques, supprimant ainsi la libération des neurotransmetteurs excitateurs. On a démontré son efficacité dans 11 études majeures en double insu, en polythérapie, chez des patients présentant des crises partielles réfractaires au traitement, avec ou sans généralisation secondaire. Des données anecdotiques subséquentes sont en faveur de son efficacité dans le traitement des absences typiques et atypiques, des secousses myocloniques, des crises toniques ou cloniques, du syndrome de Lennox-Gastaut et des spasmes infantiles. Dernièrement, la LTG a été comparée à la carbamazépine et à la phénitoïne dans des essais cliniques en double insu chez des patients chez qui on avait diagnostiqué des crises tonico-cloniques partielles et d'emblée ou secondairement généralisées. A la posologie utilisée, son efficacité était semblable à celle des médicaments plus anciens pour les crises de tout type, mais la LTG était mieux tolérée. Les effets secondaires les plus fréquents de la LTG étaient la céphalée, les nausées, la diplopie, les étourdissements, l'ataxie et le tremblement. Une éruption cutanée survient chez moins de 5% des patients. On peut en diminuer l'incidence en commençant le traitement avec une dose faible, particulièrement chez les patients qui reçoivent également du valproate sodique, qui inhibe le métabolisme de la LTG. Les inducteurs enzymatiques tels la carbamazépine, la phénytoïne et le phénobarbital accélèrent son élimination, mais la LTG elle-même n'a pas d'effet sur le métabolisme hépatique. Une interaction pharmacodynamique avec la carbamazépine nécessite une réduction de la posologie chez certains patients quand on commence le traitement par la LTG. La LTG est un nouvel agent antiépileptique qui a une demi-vie d'élimination prolongée, un large spectre d'activité et un indice thérapeutique large.

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Lamotrigine (LTG) was developed by Wellcome Laboratories in practical response to the hypothesis that a relationship existed between the antifolate effects of antiepileptic drugs and their therapeutic action.[1] Initial interest in a series of aminopyrimidines similar to pyrimethamine led to the examination of related compounds from which LTG was subsequently synthesised.

Chemical properties

LTG [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] is structurally unrelated to any other antiepileptic drugs (Figure). It is poorly soluble in water and ethanol, has a molecular weight of 256.09 and a pKa of 5.5. A number of chromatographic and immunofluorometric assays are available for its analysis in biological fluids.[2-5]

Mechanism of action

LTG stabilises presynaptic neuronal membranes by blocking voltage-dependent sodium channels and so preventing the release of excitatory amino acids, particularly glutamate and aspartate[6]. Thus, the drug ameliorates kainic acid neurotoxicity which is mediated by glutamate, but not that produced by ibotenate which is not[7]. In mouse neuroblasts, LTG inhibits high frequency sustained repetitive firing of sodium-dependent action potentials suggesting a direct effect of the drug on

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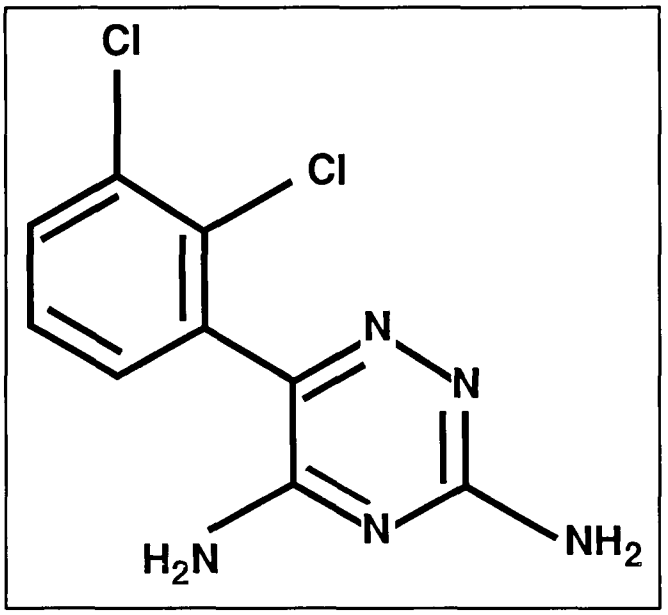

Figure: Sturcture of lamotrigine.

voltage-activated sodium channels[8]. More recent evidence supports a selective action on the slow inactivated state of the channel[9]. LTG may also influence calcium currents[10]. These mechanisms may or may not explain LTG's anti-absence and anti-myoclonic effects.

Clinical pharmacokinetics

LTG is well absorbed orally with a bioavailability approaching 100%.[11] It undergoes first order kinetics at therapeutic dosage. Peak concentrations occur 1-3 hours after oral administration. The drug is metabolised in the liver largely to the inert N-6 glucuronide conjugate, most of which is renally excreted. The elimination half-life in untreated patients ranges from 22-36 hours. It is slightly longer in the elderly[12] and in patients with Gilbert's syndrome.[13]

Efficacy

All but one of 11 pivotal crossover and parallel-group, double-blind, placebo-controlled trials have supported efficacy for LTG against partial seizures.[14] The odd study out was conducted in a small number of severely affected institutionalised patients[15]. In three reports, there were sufficient numbers of patients with secondary generalised seizures to confirm benefit for this seizure type also.[16-18] Overall, there was a 17-59% decrease in seizure numbers compared with placebo, with 7-67% of patients reporting a reduction exceeding 50%. In one study, seizure severity was found to be ameliorated by LTG.[17].These authors also reported positive changes in "mastery" and "happiness" scores, which were interpreted as improving "quality of life". A link has been suggested with this observation and LTG's ability to reduce interictal spiking and thereby improve alertness.[19]

Anecdotal evidence suggests efficacy for LTG against a range of primary generalised epilepsies, including atonic and tonic-clonic seizures, typical and atypical absences, and myoclonic jerks.[11,14] A single report exists of its successful intravenous use in abolishing status epilepticus.[20] Long-term trials support LTG's continued efficacy for up to three years with no evidence of tolerance.[11] Some patients, particularly those with severe epilepsy, report a feeling of wellbeing on LTG therapy.[19]

In some patients responding well to adjunctive lamotrigine, discontinuation of concomitant antiepileptic drugs has been successfully achieved.[14] This has been confirmed in a multicentre study of additional lamotrigine in patients not fully controlled on carbamazepine, phenytoin or sodium valproate monotherapy. The original antiepileptic drug was withdrawn in 17%, leaving these patients on LTG monotherapy.[21] A recently published double-blind comparison of LTG and carbamazepine in 260 newly diagnosed patients with partial and/or generalised tonic-clonic seizures suggested similar efficacy between the two drugs. LTG, however, was better tolerated[22]. Similar results have been reported in a smaller comparative double-blind study with phenytoin in untreated patients with recent onset epilepsy.[23]

There are relatively few data exploring the use of LTG in children.[24] However, single-blind and open studies suggest similar efficacy to that in adults across the complete range of seizure types.[11,14] There are three studies reporting promising benefit in Lennox-Gastaut syndrome.[25-27] Anecdotal data also support its value in children with infantile spasms.[28]

There has been recent interest in combining LTG with other antiepileptic drugs in patients with refractory epilepsy. Preliminary results hold out the possibility of particular efficacy for LTG with sodium valproate for generalised absence and myoclonic seizures[29-30] and for partial and tonic-clonic seizures[31] and with vigabatrin for partial seizures.[32]

Adverse experiences

The commonest side-effects with LTG are headache, nausea and vomiting, dizziness, ataxia and tremor.[33] Sedation is not a common problem.[34] Aggression, irritability, agitation, confusion, hallucinations and psychosis have occurred in a few patients, but this appears to represent background incidence rather than a drug-related phenomenon. A small number of deaths in patients taking a combination of antiepileptic drugs including LTG can be attributed to a complication of seizure activity, as the clinical picture included prolonged fitting, disseminated intravascular coagulation and multi-organ failure.[35] There is no evidence of teratogenesis with LTG, although it is early days yet.

Rash is the commonest reason for discontinuing LTG treatment. It is estimated to complicate the management of 3-5% of exposed patients.[34] It occurs in the first few months of treatment and is usually maculopapular. If mild, it may subside spontaneously or on reducing the dose. Successful rechallenge may be possible.[36] Some patients, however, develop an accompanying systemic illness with fever, arthralgia, myalgia, lymphadenopathy and eosinophilia. There is good circumstantial evidence that introduction of LTG at low dosage substantially reduces the likelihood of rash (Brodie et al - in preparation). Interestingly, this has been suggested previously for the rashes associated with carbamazepine and phenytoin administration.[37] Rarely, a more severe skin eruption with bullous erythema multiforme or Stevens Johnson syndrome complicates LTG use.[38] A single case of reversible neutropenia associated with rash and fever has been published.[39]

Drug interactions

LTG does not itself influence the metabolism of other lipid soluble drugs including that of the components of the oral

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contraceptive pill and warfarin.[40] Acetominophen has been reported to accelerate its metabolism by an unknown mechanism.[41] LTG concentrations are profoundly affected by the presence or administration of other antiepileptic drugs.[42] Enzyme inducers, such as phenobarbital, carbamazepine and phenytoin, reduce its elimination half-life from a mean of 29 to around 15 hours. Sodium valproate, an inhibitor, lengthens it to about 60 hours. The combined effects of an inducer and inhibitor tend to cancel each other out! In practice, problems are unlikely to be encountered when LTG is introduced so long as the dose is tailored against the response and the emergence of side-effects. However, valproate withdrawal will produce a fall in LTG concentration, whereas when an inducer is discontinued, the LTG level can be expected to rise.[43]

Fianlly, a pharmacodynamic interaction is a common consequence when LTG is introduced in patients established on high dose carbamazepine.[44] Symptoms of neurotoxicity (headache, nausea, dizziness, diplopia, ataxia) can be ameliorated by reduction of the carbamazepine dosage. LTG does not increase the circulating carbamazepine concentrations nor those of its active metabolite carbamazepine 10,11 epoxide.[32] Pretreatment with LTG has no effect on the metabolism of a single dose of carbamazepine epoxide.[45] Patients taking carbamazepine should be warned of this possible interaction and advised to reduce their carbamazepine dose if they develop symptoms.

Concentration monitoring

There are few data investigating the clinical utility of measuring circulating LTG concentrations.[46] Those required to elicit an adequate response to the drug vary widely among patients. There is no evidence either that side-effects are more likely to occur in patients with high LTG levels.[38] Indeed, some individuals appear to benefit from as much as 1000mg LTG daily without complaint, whereas others develop a headache or nausea on a dose as low as 100mg. In a recently completed concentration-effect-toxicity study, seizure control for at least 6 months was achieved at LTG concentrations ranging from 1.4 to 18.7mg/L and central nervous toxicity responding to reduction in dose presented at levels between 0.4 and 18.5mg/L.[47] The authors concluded that no useful concentration-effect or concentration-toxicity relationship with LTG could be demonstrated, and so routine therapeutic drug monitoring could not be recommended.

Practical use

Lamotrigine is licensed in more than 70 countries worldwide as adjunctive therapy in patients experiencing refractory partial seizures with or without secondary generalised seizures. It has recently become available in Canada and the USA for this indication. In some countries it has been approved for use in children and as monotherapy. LTG is usually prescribed twice a day, but a single daily dose can be employed in patients taking the drug with sodium valproate or as monotherapy. There is, as yet, no parenteral formulation. A low, slow titration schedule will reduce the likelihood of rash. The starting dose depends on existing treatment when the drug is used as adjunctive therapy. A suggested schema is outlined in the Table 1. The schedule for LTG's use as monotherapy has been included for completion. In patients who tolerate the drug particularly well, doses exceeding 1000mg daily have been tried with benefit.

Table 1 Lamotrigine dosage and titration schedule

1. Add-on in treated adults and adolescents

	Valproate	Others
Weeks 1-2	12.5mg daily	50mg daily
Weeks 3-4	25mg daily	50mg twice daily
Maintenance	50-100mg twice daily	100-200mg twice daily

2. Add-on in treated children

	Valproate	Others
Weeks 1-2	0.2mg/kg	2mg/kg
Weeks 3-4	0.5mg/kg	5mg/kg
Maintenance	1-5mg/kg	5-15mg/kg

3. Monotherapy in newly diagnosed epilepsy

	Adults	Children
Weeks 1-2	25mg daily	0.5mg/kg
Weeks 3-4	25mg twice daily	1mg/kg
Maintenance	50-100mg twice daily	2-8mg/kg

Higher doses can be tried if seizures persist and the patient is tolerating the drug without complaint.

Published placebo-controlled trials with LTG have been confined so far to patients with partial seizures with or without secondary generalisation and those with idiopathic tonic-clonic seizures. However, the drug also seems effective across the range of other generalised epilepsies, in the Lennox-Gastaut syndrome and in infantile spasms. Its use in combination with sodium valproate and vigabatrin shows promise in refractory epilepsy.

Like other antiepileptic drugs, LTG will exacerbate seizures in a small number of patients in whom it should be rapidly withdrawn. Reducing the dose by 50 to 100mg weekly increments is a reasonable policy.[43] As LTG is broken down by hepatic glucuonidation, it seems sensible to avoid its use in patients with severe liver disease. Routine monitoring of LTG concentrations is not necessary.

Therapeutic potential

A major international programme of clinical research with LTG is underway. Although effective against partial seizures, LTG seems to be particularly beneficial in patients with the primary generalised epilepsies. Good results are being reported too in patients with learning disabilities who have a range of seizure types. Controlled trials in children and in Lennox Gastaut syndrome are in progress, as are double-blind comparative studies against sodium valproate in the primary generalised epilepsies and against carbamazepine in the elderly. Double-blind comparative trials with LTG as monotherapy in newly diagnosed epilepsy suggest that the drug will have an important place in this patient population. LTG's long elimination half-life, broad spectrum of activity and wide therapeutic ratio make it an attractive proposition for this indication. Preliminary data hold out the possibility that it will not be teratogenic. Rational duotherapy with a regimen containing LTG in refractory partial seizures and for the primary generalised epilepsies is an exciting prospect for future clinical research.[48]

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