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AN OVERVIEW ON LAMOTRIGINE

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ABSTRACT

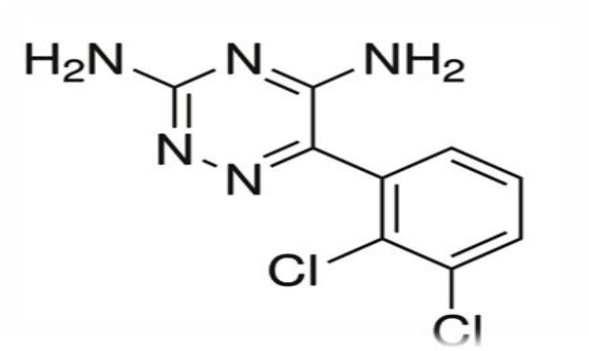
Lamotrigine (LTG) was first synthesized in the early 1980s. It was approved for adult use in Ireland in 1990, the UK in 1991, and by the US Food and Drug Administration (FDA) in 1994. LTG is an organic compound, white to pale-cream colored powder with chemical name 6-(2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine. LTG stabilizes presynaptic neuronal membranes by acting at voltage-sensitive sodium channels and modulating presynaptic transmitter release of excitatory neurotransmitters such as aspartate and glutamate. LTG with enzyme inducing AEDs like PHT, recommended initial dose is 50mg/day for 2 weeks, followed by 50mg three times a day for 2 weeks. There are several reports of pharmacokinetic interactions of oral contraceptives with AEDs, which raise concern regarding increased risk of seizures. Some oral contraceptives decrease serum AED concentration by increasing AED metabolism. LTG in the treatment of pediatric patients: LTG in the treatment of childhood absence seizures: In a retrospective analysis, patients with typical absence seizures refractory to VPA were treated with low-dose of LTG and treatment appeared to be effective

KEYWORDS: lamotrigine; anti-epileptic, valproic acid.

INTRODUCTION

Lamotrigine (LTG) was first synthesised in the early 1980s. It was approved for adult use in Ireland in 1990, the UK in 1991, and by the US Food and Drug Administration (FDA) in 1994.[1] Since its market authorisation over two decades ago, it has been used increasingly for the treatment of paediatric epilepsy. It is the most commonly prescribed new generation antiepileptic drug (AED), accounting for 65% of new AED prescriptions in the UK[2] and 12% of all AED prescriptions for children in the Netherlands.[3] In the UK, LTG is recommended as monotherapy as the first-line treatment for newly diagnosed focal seizures

and as an adjunct for refractory focal seizures in children.[4] It is a second-line monotherapy drug for new onset generalised seizures and a useful adjunct for refractory generalised seizures. It is the third drug of choice, after ethosuximide and valproate, for absence seizures and it may be administered as a monotherapy or polytherapy.[4] Dosing of LTG in children on adjunctive therapy is dependent on the effect of the coadministered drug. Higher doses may be required when coadministered with AEDs, such as phenobarbital, phenytoin, carbamazepine and oxcarbazepine, which have been shown to increase the drug's clearance and reduce its plasma concentration. Conversely, valproic acid reduces LTG clearance and raises its plasma concentration by as much as twofold; hence, a lower dose is recommended.[5] A safety concern with LTG in children is the occurrence of a skin rash. This can vary in intensity, from transient mild rash to Stevens-Johnson's syndrome (SJS), which can be fatal.[6] Children are generally more Strengths and limitations of this study ▪ This systematic review assessed the quality of all the prospective studies. ▪ Randomised controlled trials (RCTs), cohort studies and case reports were reviewed. ▪ Only a limited number of RCTs of lamotrigine in children have been published, thus limiting the power of the meta-analysis. ▪ The risks of adverse reactions between monotherapy and polytherapy users were compared in RCTs alone because only one prospective cohort study involving children receiving lamotrigine monotherapy was identified. Egunsola O, et al. LTG can worsen myoclonic seizures and is usually avoided in patients with severe myoclonic epilepsy of infancy (Dravet syndrome).[8] This systematic review was performed to identify all studies of LTG safety in children, to determine the adverse reactions of LTG and to compare the safety of the drug with other AEDs.



Chemistry and Structure: LTG is an organic compound, white to pale-cream coloured powder with chemical name 6- (2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine. It comes under the class phenyltriazine, structurally unrelated to other anti-epileptic drugs. Its molecular formula and molecular weight is C9H7Cl2N5 and 263.09g/mol respectively. It is

having a solubility of 0.17mg/ml and 4.1mg/ml at 25ºC in water and 0.1M HCl respectively with pKa of 5.7. The 5 drug is commercially supplied as tablets for oral administration in various strengths like 5, 25, 50, 100, 150 and 200mg.[10,11]

Mode of action: LTG stabilises presynaptic neuronal membranes by acting at voltage-sensitive sodium channels and modulating presynaptic transmitter release of excitatory neurotransmitters such as aspartate and glutamate. In-vitro studies on rat cerebral cortex demonstrated ability of LTG in the inhibition of veratrine (sodium channel activator) induced aspartate, glutamate and it is found to be less effective in the inhibition of GABA or acetylcholine release without affecting potassium induced amino acid release. In conclusion, these studies suggest that LTG acts presynaptically at voltage-sensitive sodium channels.[12] In another study on mouse neuroblasts, LTG inhibited repetitive and sustained firing of sodium dependent action potentials suggesting its direct effect on voltage-activated sodium channels.[13] LTG may also influence and inhibit N- and P-type calcium currents in cortical neurons. These studies help in providing additional information on LTG and its anti-epileptic action at synaptic level.[14,15] LTG has broad spectrum of activity against various seizures like absence seizures, focal seizures, tonic-clonic seizures and juvenile myoclonic epilepsy (JME) which was demonstrated in various animal preclinical studies. Seizures were induced in rats and mice using pentylenetetrazol (PTZ) infusion and repeated maximal electroshock (MES) methods, and when treated with LTG, termination of hind limb extension was observed, suggesting activity against focal seizures and tonic-clonic seizures. However at higher LTG doses, clonus latency was not increased in the PTZ test, suggesting ineffectiveness against absence seizures. But, in other models more predictive of human absence seizures, including the 6 photically evoked after-discharge test model in rats and the lethargic (lh/lh) mouse model, LTG was effective. LTG decreased electrically induced cortical after-discharge and hippocampal after-discharge duration in the marmoset, rat and dog, providing additional evidence of its efficacy against focal and dyscognitive seizures,[16,17,18]

Pharmacokinetics: LTG has a half-life (t½) of 24-34h in healthy individuals. It is highly metabolised by the liver enzymes, UDP-glucuronosyltransferase 1-4 and UDP-glucuronosyltransferase 1-3 involving glucuronic acid conjugation.[18] LTG undergoes hepatic metabolism predominantly by glucuronic acid conjugation. UD Pglucuronosyltransferase 1-4 and UDP-glucuronosyltransferase 1-3 are the two major enzymes 7 involved in the LTG metabolism.[19] 70% of the oral LTG is recovered in urine as

metabolite conjugate, LTG-2-N-glucuronide.[20] This increase in rate of clearance and decrease in t½ (~ 14h) of LTG on concurrent administration with other anti-epileptic drugs (AEDs) might be due to induction of hepatic cytochrome P450 enzyme by these drugs. To avoid this, the dose of LTG should be decreased or increased in presence of enzyme inhibitors or inducers as clinically indicated (testing of serum concentrations).[21]

Interactions: There are several reports of pharmacokinetic interactions of oral contraceptives with AEDs, which raise concern regarding increased risk of seizures. Some oral contraceptives decrease serum AED concentration by increasing AED metabolism. AED like LTG is affected by enzyme inducer and enzyme inhibitor drugs. It interacts with them and results in serum level fluctuations. Drugs like PHT, fosphenytoin, PHB, primidone, oxcarbazepine and olanzapine increases LTG metabolism and results in reduced serum levels, whereas enzyme inhibitors like valproic acid, fluoxetine and sertraline inhibit LTG metabolism, resulting in raised serum levels.[22]

Dosing: Dosing LTG has no well-defined therapeutic range and its dosing differs from patient to patient depending on the concomitant use with an enzyme-inducing or enzyme-inhibiting AEDs. So based on patients clinical response and/or adverse effects, dose adjustments should be done to establish a safe therapeutic plasma level.[23,24] LTG with enzyme inducing AEDs like PHT, recommended initial dose is 50mg/day for 2 weeks, followed by 50mg t.i.d. for 2 weeks. Therefore, depending on the patient clinical response, further dose increases can be made up to 100 – 500mg/day (1 or 2 divided doses) for the usual maintenance. 27 In patients receiving LTG with enzyme inhibiting AEDs like VPA, an initial dose of 25mg every other day is recommended for 2 weeks, followed by 25mg daily for 2 weeks. Further dose is increased to 25 – 50mg/day every 2 weeks up to a maximum dose of 300 – 500mg/day. Maintenance doses as high as 700 mg/day have been used. However relationship between plasma concentration and clinical response and/or adverse effects is not yet clear, although a clinically applicable therapeutic range of drug plasma concentration is 3 – 14 mg/l.[25] The value of routine monitoring of LTG plasma concentration is not yet established but it should be followed stringently in pregnant women.[23,24,26]

Indications

LTG in the treatment of paediatric patients: LTG in the treatment of childhood absence seizures: In a retrospective analysis, patients with typical absence seizures refractory to VPA

were treated with low-dose of LTG and treatment appeared to be effective.[27] In children and adults, 1.6 – 3mg/kg/day and 25 – 50mg/day of VPA was added to differing doses of LTG.

LTG in the treatment of tonic-clonic seizures: In an unblinded randomised controlled trial by SANAD in hospital-based outpatient clinics in UK, study was aimed to compare the longer-term effects of VPA, LTG, or topiramate in patients with tonic-clonic onset seizures or seizures that are difficult to classify.

LTG in the treatment of Lennox Gastaut syndrome and Juvenile myoclonic epilepsy: LTG was proved to be effective in the treatment of JME and seizures associated with Lennox–Gastaut syndrome. In a double-blind, placebo-controlled, randomised trial, LTG was used as add-on therapy in patients with Lennox–Gastaut syndrome.[28]

Role and effect in psychiatry: LTG was initially developed as an anticonvulsant drug but later it emerged as new drug in psychiatry.[29] It is used as mood stabiliser and established for the treatment of bipolar disorders by the end of 1990s. Many clinical trials have confirmed its activity in bipolar maintenance treatment to prevent relapse to both depressive and manic phases in patients aged 18years and over.[30] LTG is currently licensed for the maintenance treatment of bipolar disorder (depressive episodes in bipolar type II).

Role and effect on cognitive function: Association of anti-epileptic therapy with cognitive impairment represents a particular problem, especially in the young and elderly. Existing data suggest that LTG is an effective, well tolerated new generation AED.

Role and effect on neuronal damage: Status epilepticus causes neuronal damage and cognitive impairment. In a study on wistar rats for 2 weeks, LTG was compared with CBZ for their effect on status epilepticus-induced temporal lobe damage and memory impairment.
Role and effect on women and pregnancy Among all the AEDs and mood stabilisers, CBZ and valproic acid are widely used.

Adverse effects

The side effect profile is different for different patients. The most common side effects associated with LTG are dizziness, nausea, vomiting, headache, tremor, and ataxia. In few cases like JME, LTG can increase seizure frequency and background incidences along with irritability, confusion, aggression, agitation, psychosis, hallucination, and rarely sedation. Death is a very rare phenomenon seen in patients taking LTG as monotherapy or in

combination with other AEDs; it can be attributed to complication of seizure activity, as the clinical picture included disseminated intravascular coagulation, multi-organ failure. LTG was also linked to increased risk of Sudden Unexpected Death in Epilepsy (SUDEP) and pregnancy-related deaths. As per FDA guidelines from December 2010, LTG carries a black box warning about aseptic meningitis and life-threatening skin reactions like Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, toxic epidermal necrolysis, and Stevens– Johnson syndrome.[31,32,33,34]

Abbrevations

Lamotrigine (LTG)

US Food and Drug Administration (FDA)

Antiepileptic drug (AED),

Unexpected Death in Epilepsy (SUDEP)

Stevens-Johnson's syndrome (SJS)

Randomised controlled trials (RCTS)

Pentylenetetrazol (PTZ)

Juvenile myoclonic epilepsy (JME)

Maximal electroshock (MES)

Juvenile myoclonic epilepsy (JME)

Valproic acid (VPA)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

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