Research Review
PRODUCT REVIEW

Levetiracetam [Levetiracetam-Rex]

About the Reviewer

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After undergraduate training in medicine at the University of Tasmania, Elizabeth trained in neurology at Auckland Hospital. Post graduate training consisted of an EEG/epilepsy Fellowship, followed by EMG training at the Mayo Clinic, Rochester Minnesota. She then returned to Auckland and has been a member of the Department of Neurology, as well as head of Clinical Neurophysiology and a member of the Epilepsy Surgical Group.

Elizabeth has had an active interest in epilepsy and helped to establish the national centre for surgical treatment of epilepsy at Auckland Hospital. The Epilepsy Surgical Group at Auckland Hospital, consisting of both adult and paediatric epileptologists, provides a tertiary referral service for surgical treatment of epilepsy in New Zealand, as well as providing a diagnostic service for patients with refractory epilepsy. Elizabeth is the current secretary of the New Zealand branch of the ILAE.

This review discusses the evidence in support of the use of levetiracetam, an established broad-spectrum second-generation antiepileptic drug (AED). This agent is now available in New Zealand and is fully funded by PHARMAC.

Epilepsy

Epilepsy, a common serious neurological disorder affecting both adults and children, is characterised by recurrent seizures caused by abnormal neuronal discharges in the brain.[1-3] Such seizures may be broadly categorised as either partial onset seizures (sometimes called focal seizures) or generalised onset seizures.[1-3] Partial onset seizures originate in and/or are restricted to a localised area of the brain.[1-3] This type of seizure may be further classified as simple partial, complex partial or partial with secondary generalisation (resulting from the spread of the seizure to the entire brain). The symptoms associated with partial onset seizures are determined by the location of the abnormal neuronal discharge.[1-3] In contrast, generalised onset seizures are characterised by more diffuse neuronal discharges affecting both brain hemispheres at the onset of the seizure.[1-3] These seizures are further classified into tonic, clonic, atonic, myoclonic and/or absence seizures, according to the presence or absence of different phenomena.[1-3] The term epileptic syndrome refers to a cluster of signs and symptoms and is used to describe epilepsy in patients who experience more than one type of seizure (partial, generalised or unclassifiable) together or in sequence.

In approximately 30-60% of epilepsy cases the aetiology of the disorder cannot be identified (idiopathic or cryptogenic epilepsy). In those cases where the cause can be identified, the top four most frequently reported aetiologies of epilepsy in developed countries are trauma, central nervous system infections, cerebrovascular disorders and perinatal risk factors.[4] Many environmental, genetic, physiological and pathological factors may be involved in the development of epilepsy, and a family history of the disorder is known to enhance most risk factors.[4] This is especially true for idiopathic epilepsy.[4]

Incidence and prevalence

The incidence of epilepsy in developed countries is estimated to be approximately 50 cases per 100 000 people per year, with an estimated global prevalence of approximately 40 million; over half of these cases involve individuals with partial seizures.[1,4,5] In New Zealand, the epilepsy prevalence is about 0.6%, similar to that of other Western nations.[6,7] This equates to approximately 25 000 New Zealanders with active epilepsy at any one time.[7]

The burden of epilepsy

Epilepsy is associated with increased morbidity and mortality, including unexpected deaths without a clear cause,[8,9] and the World Health Organisation (WHO) estimated global rate of death due to epilepsy in 2004 was approximately 0.2%.[5] Epilepsy consists of more than seizures for the affected individual and their family, having psychological, economic and social repercussions. The dramatic and alarming clinical features of seizures frequently elicit fear and misunderstanding.[4] Within the wider community there is considerable ignorance about epilepsy and an unacceptable level of prejudice against individuals with the disorder.[6] Many patients with epilepsy are socially disadvantaged and often have difficulty obtaining jobs.[6] Individuals with epilepsy commonly encounter problems with driving, personal development, and social and personal relationships. It is therefore not surprising that depression is a serious and frequent comorbidity of epilepsy.[10]

Diagnosis

An accurate diagnosis of epilepsy is fundamentally important, but confident diagnosis or exclusion is difficult because seizure types vary and there may be no accompanying neurological signs. Furthermore, other conditions such as pseudoseizures and syncope may be confused with epileptic seizures.[4] Diagnosis should therefore be confirmed by a professional with expertise in epilepsy. Diagnostic imaging modalities, including MRI and CT, and an EEG are helpful to clarify seizure type.[4]

Treatment options

Epilepsy is mainly treated with antiepileptic drugs (AEDs). This pharmacological treatment approach endeavours to ensure freedom from seizures without interfering with normal cognitive function and development, and with minimal adverse effects.[1,2,11]

Although AED monotherapy controls seizures in many patients, approximately 30% of patients may require treatment with multiple AEDs and some patients will continue to experience seizures even when receiving multiple AEDs.[12] In patients with severe refractory epilepsy and established seizure-related disability it may be necessary to consider resective or palliative surgery.[13]

Pharmacological treatment options include a wide range of older AEDs (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone and valproate), as well as the newer second-generation agents (levetiracetam, gabapentin, lacosamide, lamotrigine, oxcarbazepine, pregabalin and topiramate). In general, the efficacy of the newer AEDs appears to be similar to that of the older AEDs.[14] However, the new agents such as the broad-spectrum AED, levetiracetam, appear to offer improved tolerability, simpler titration and administration regimens, and a lower risk of interactions with other medications.[1,2,15]

About levetiracetam

In New Zealand, Levetiracetam is currently approved by Medsafe for use in epileptic patients ≥6 years of age, as add-on therapy in the treatment of partial onset seizures with or without secondary generalisation.[16] In Australia, levetiracetam is approved for use in the following: patients ≥4 years of age as add-on therapy for partial onset seizures; patients ≥4 years of age as add-on therapy for patients with idiopathic epilepsy experiencing primary generalised tonic-clonic seizures; patients from 16 years of age as monotherapy for partial onset seizures in newly-diagnosed epilepsy; as add-on therapy for myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy.[17]

In New Zealand, Rex Medical Ltd's brand of levetiracetam [Levetiracetam-Rex] is fully subsidised by PHARMAC without the requirement for Special Authority approval.

Levetiracetam has shown efficacy in the following settings: as adjunctive therapy for controlling seizures in children and adults with partial onset seizures with or without secondary generalisation; as adjunctive therapy in patients with idiopathic generalised epilepsy with generalized tonic-clonic seizures or myoclonic seizures; and as monotherapy for adults with newly diagnosed partial onset generalised tonic-clonic seizures.[14]

Levetiracetam has a favourable tolerability profile and the majority of adverse events associated with its use appear to be mild-to-moderate.[14,18] Furthermore, the agent does not exhibit clinically significant interactions with other drugs and therapeutic drug monitoring is not required.[14,18]

The most common side-effect is behavioural or mood changes, which can occur in up to 10% of patients.[14,16]

Pharmacological properties

Levetiracetam, a pyrrolidone derivative, is chemically unrelated to other available AEDs and its mechanism of action is not yet fully understood. It is known that the agent binds to a synaptic vesicle protein, SV2A, and modulates synaptic vesicle exocytosis, causing direct inhibition of presynaptic neurotransmitter release.[19,20] Levetiracetam also reduces the release of calcium from intraneuronal stores, partially inhibits the N-type calcium channel and opposes the activity of the negative allosteric modulators β-carbolines and zinc on GABA- and glycine-gated currents.[18]

Levetiracetam is a permeable and highly soluble compound with a linear pharmacokinetic profile.[16] The oral bioavailability of levetiracetam is almost 100% and peak plasma concentrations (C_{max}) are reached 1.3 hours after administration.[16] Steady state is achieved after twice daily dosing for two days.[16] The half-life of levetiracetam in adults is approximately 7 hours.[14] The main metabolite of levetiracetam, ucb L057, is pharmacologically active and renal clearance is the major route of elimination.[14,16]

Paediatric patients exhibit a similar pharmacokinetic profile for levetiracetam to that seen in adults.[14] However, in epileptic children aged 5-12 years, the apparent body clearance of the agent is approximately 30% higher than in adults, with a half-life of approximately 6 hours.[16]

In the elderly, the half-life of levetiracetam is approximately 10-11 hours and this is due to decreased renal function in this population.[16]

Dosage and administration[16]

Levetiracetam film-coated tablets must be taken orally, swallowed with liquid. They may be taken with or without food. The daily dose is to be administered in two equal dose amounts (ie. 2 x 250 mg or 2 x 500 mg) and the tablets are not to be divided.

Adults and adolescents (aged 12-17 years) weighing ≥50 kg: therapeutic dose is 500 mg twice daily as adjunctive therapy (this dose may be started on the first day of treatment). The dose may be increased up to 1500 mg twice daily; maximum recommended daily dose is 3000 mg. Dose alterations can be made in 500 mg twice daily increments or decrements every 2-4 weeks.

Elderly (≥65 years) patients with compromised renal function should have their dose adjusted (see Medsafe datasheet for dosage schedule based on renal function).

Children (aged 6-11 years) and adolescents (aged 12-17 years) of <50 kg: initial therapeutic dose is 10 mg/kg twice daily and may be increased up to 60 mg/kg/day (in two 30 mg/kg doses). The lowest effective dosage should be used and dose alterations can be made in 10 mg/kg twice daily increments or decrements every 2 weeks. Recommended dosing is as follows:

Children weighing 25 kg: starting dose = 250 mg twice daily; maximum dose = 750 mg twice daily.

Children >50 kg: the dosage is the same as in adults (starting dose = 500 mg twice daily; maximum dose = 1500 mg twice daily).

Infants and children <6 years of age: levetiracetam tablets are not recommended for this age group.

Patients with renal impairment may require dose adaptation (see Medsafe datasheet).

For patients with severe hepatic impairment and a creatinine clearance <70 mL/min, a 50% reduction of the daily maintenance dose is recommended.

SPECIALIST COMMENTARY ON CURRENT TREATMENTS

Clinical efficacy and safety of levetiracetam in the treatment of epilepsy

Multicenter double-blind, randomized, placebo controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group[21]

Authors: Shorvon SD et al

Summary: The efficacy and tolerability of levetiracetam as add-on therapy in patients with refractory partial seizures was investigated in this European multicentre, double-blind, randomised, placebo-controlled trial. A total of 324 patients with uncontrolled simple or complex partial seizures, or both, with or without secondary generalisation received add-on therapy with levetiracetam 500 mg or 1000 mg twice daily or placebo. Following enrollment, the groups were assessed during a baseline period of 8 or 12 weeks, followed by a 4-week titration period. The evaluation period was 12 weeks. Compared with placebo, levetiracetam 1000 mg/day and 2000 mg/day significantly decreased partial seizure frequency, with a reduction in seizure frequency of ≥50% occurring in 10.4%, 22.8% and 31.6% of patients, respectively. The most commonly reported adverse events in levetiracetam recipients were headache, asthenia and somnolence. However, the incidence of adverse events was not significantly different between the three groups (placebo group = 73.2%; 1000 mg/day group = 70.8%; 2000 mg/day group = 75.5%). Furthermore, plasma concentrations of concomitant antiepileptic drugs, vital signs or laboratory parameters were not affected by the administration of levetiracetam.

Comment: This was the first major randomised study to demonstrate efficacy in the difficult group of patients with simple or complex partial seizures. An important observation was that the drug was commenced at 1000 mg per day, suggesting that it can be introduced at an effective dose without the slow titration usually required in add on anti-epileptic drugs. In addition, it was well tolerated with few significant side-effects and had no major drug interactions.

Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy[22]

Authors: Berkovic SF et al

Summary: The efficacy and tolerability of levetiracetam as adjunctive therapy in patients with uncontrolled generalised tonic-clonic seizures associated with idiopathic generalised epilepsies was investigated in this multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The study screened 229 adults and children (aged 4-65 years) with idiopathic generalised epilepsy during an 8-week baseline period (4-week retrospective and 4-week prospective). Those patients experiencing ≥3 generalised tonic-clonic seizures during the baseline period, despite receiving stable doses of one or two AEDs, were randomised to receive either placebo (n = 84) or levetiracetam (n = 80) at a target dose of 3000 mg/day for adults and 60 mg/kg/day for children during a 4-week titration period and a 20-week evaluation period. Compared with placebo, levetiracetam recipients experienced a significantly ($p = 0.004$) greater mean reduction in generalised tonic-clonic seizure frequency per week during the treatment period (28.2% vs 56.5%). The percentage of responders (≥50% reduction in generalised tonic-clonic seizure frequency per week) was significantly ($p < 0.001$) greater in the levetiracetam group than the placebo group (72.2% vs 45.2%; OR 3.28: 95% CI 1.68–6.38). During the first 2 weeks of treatment, 64.6% of levetiracetam recipients were classified as responders, compared to 45.2% on placebo ($p = 0.018$). Among the levetiracetam recipients, 34.2% were free from generalised tonic-clonic seizures and 24.1% were free from all seizure types during the 20-week evaluation period; this compared with 10.7% and 8.3% of placebo recipients ($p < 0.01$). While 4.8% of placebo recipients discontinued therapy due to adverse events during the study period, only 1.3% of levetiracetam recipients discontinued therapy, indicating that the agent was well tolerated.

Comment: This study followed an earlier study in idiopathic generalised epilepsy with myoclonic seizures. Both studies showed efficacy in medically refractory idiopathic generalised epilepsies, including epilepsy with myoclonic seizures. This study used a higher dose of levetiracetam than the studies in partial epilepsy, and also included children. This higher dose was well tolerated. There was a rapid onset of action with many of the responders showing efficacy at 1000 mg per day. Importantly, a significant percentage of patients were seizure free, with all seizure types being improved. These two studies have led to levetiracetam being considered early in the treatment of idiopathic generalised epilepsy. This study also documented the problematic side-effect of irritability and mood alteration, along with the previously documented side-effects of fatigue, somnolence and headache.

Newer-generation antiepileptic drugs and the risk of major birth defects[23]

Authors: Mølgaard-Nielsen D and Hviid A

Summary: This large population-based cohort study, published in JAMA, investigated the risk of major birth defects with foetal exposure to newer-generation AEDs during the first trimester of pregnancy. Records from a total 837 795 live-born infants in Denmark from January 1st 1996 through September 30th 2008 were reviewed. Nationwide health registries were used to ascertain maternal use of AEDs, birth defect diagnoses and potential confounders. A total of 1532 infants had been exposed to levetiracetam, lamotrigine, oxcarbazepine, topiramate or gabapentin during the first trimester, while 836 263 had not been exposed to an AED. Major birth defects were evident in 3.2% of those exposed to AEDs compared with 2.4% not exposed to such agents; this difference was not significant (adjusted prevalence OR 0.99; 95% CI 0.72–1.36). While a major birth defect occurred in 2.8% – 4.6% of those exposed to lamotrigine, oxcarbazepine or topiramate, such birth defects were not seen in those exposed to levetiracetam (n = 58) and were uncommon (1.7%) in those exposed to gabapentin (n = 59) during the first trimester.

Comment: Although the number of women who had pregnancies whilst on levetiracetam in this study is too small to be significant, there is accumulating evidence from other pregnancy registers that there is no major increase in major foetal malformations above that of the other AEDs. This drug is being increasingly used instead of valproate for idiopathic generalised epilepsies in women of child-bearing age.

Child development following in utero exposure: levetiracetam vs sodium valproate[24]

Authors: Shallcross R et al

Summary: In this observational study, early cognitive development was assessed in children (aged <24 months) exposed in utero to levetiracetam (n = 51) or sodium valproate (n = 44), and in a group of children representative of the general population (controls; n = 97). The study population was recruited prospectively from the UK Pregnancy and Epilepsy register, and children were assessed using the Griffiths Mental Development Scale (1996). Children exposed to levetiracetam did not significantly differ from control children in overall developmental ability, but exhibited significantly ($p < 0.001$) higher developmental scores when compared to children exposed to sodium valproate. For overall development quotient, those with levetiracetam exposure exhibited significantly ($p < 0.001$) higher scores than those exposed to sodium valproate. While 40% of children exposed to sodium valproate fell within the below average range (developmental quotient score <84), only 8% of those exposed to levetiracetam fell within this range (the corresponding value for controls was 12%). The RR of delayed development for sodium valproate-exposed children was 3.38 in comparison to children exposed to levetiracetam. Levetiracetam exposure in utero was not shown to be associated with outcome according to linear regression analysis controlling for maternal epilepsy and demographic factors.

Comment: Data showing cognitive delay in children exposed to valproate in utero has led to examination of alternative AEDs which can be used safely during pregnancy. The broad spectrum efficacy of levetiracetam as well as this early data suggesting there is no major risk of cognitive impairment, has led to increasing use of levetiracetam in pregnancy and in women of child-bearing age. More data is needed to make a confident recommendation.

Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy[25]

Authors: Arif H et al

Summary: The efficacy of AEDs in older patients (≥50 years) with epilepsy was investigated in this retrospective review. The records of 417 such patients who were taking any of the ten most commonly prescribed AED between 2000 and 2005 were reviewed. AEDs included the following; levetiracetam, lamotrigine, carbamazepine, gabapentin, oxcarbazepine, clobazam, phenytoin, topiramate, valproate sodium and zonisamide. The mean age was 66 years and 77.6% of patients had localisation-related epilepsy. Overall, 78.8% of patients remained taking at least one AED for 1 year. No significant non-AED predictors of retention (taking the AED for ≥12months) were identified. Lamotrigine and levetiracetam had the highest 12-month retention rates (79% and 73%, respectively), while oxcarbazepine had the lowest rate at 24%. Lamotrigine and levetiracetam also had the highest 12-month seizure-freedom rates (54% and 43%). The most common intolerable adverse effects were imbalance, drowsiness, and gastrointestinal symptoms.

Comment: This study confirms that levetiracetam is efficacious and well-tolerated in older patients. Its lack of interaction with other medication and good tolerability make this a useful drug to consider in the older adult presenting with epileptic seizures.

The Effect of Antiepileptic Drugs on Cognition: Patient Perceived Cognitive Problems of Topiramate versus Levetiracetam in Clinical Practice[26]

Authors: Bootsma HP et al

Summary: The impact of levetiracetam and topiramate on cognitive function were compared in this study involving 402 patients from the epilepsy centre Kempenhaeghe, The Netherlands. A total of two hundred and sixty patients received topiramate and 142 received levetiracetam. Cognitive complaints were assessed after 6, 12 and 18 months of treatment using patient perceived problems as a primary outcome measure. A statistically significant ($p = 0.04$) difference in retention at 18 months was evident, with 15% more levetiracetam recipients continuing treatment than topiramate recipients (18-month retention; 61% vs 46%). At the 6-month assessment, significantly ($p = 0.04$) more patients in the topiramate group had neurocognitive complaints compared with levetiracetam recipients (15% vs 4%); at 12 and 18 months there was no significant difference between the two groups.

Comment: Cognitive side-effects of AEDs are always a concern, especially in children. This was a retrospective review of a large cohort of patients, both adult and children taking either topiramate or levetiracetam. Although detailed neuropsychological assessment was not performed, levetiracetam had a better retention rate and much fewer cognitive side-effects than topiramate.

Experts' concluding remarks

Levetiracetam is the first new anti-epileptic drug to be registered and funded in New Zealand for some years. It has the advantages of being very well tolerated with no major drug interactions. It is effective in a broad spectrum of seizure disorders, including seizures of partial onset and idiopathic generalised seizure disorders. The ability to start the drug at an effective dose, as well as its lack of interactions with other medications has led to its increasing use as an AED of first choice in patients with complex disorders, such as cancer patients on chemotherapy, and neurosurgical patients. The favourable data on foetal outcome of pregnancies exposed to levetiracetam, and the increasing concern about the use of Epilim in pregnancy, have led to this drug being used increasingly as a first-line agent in young women of child-bearing age, particularly those with idiopathic generalised epilepsy. It is generally tolerated well, but behavioural changes, agitation, irritability and depression can develop quite rapidly and may limit its use in a small but significant number of patients.

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