Levetiracetam in the treatment of epilepsy

Bassel Abou-Khalil

Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Abstract: Epilepsy is a common chronic disorder that requires long-term antiepileptic drug therapy. Approximately one half of patients fail the initial antiepileptic drug and about 35% are refractory to medical therapy, highlighting the continued need for more effective and better tolerated drugs. Levetiracetam is an antiepileptic drug marketed since 2000. Its novel mechanism of action is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain. Its pharmacokinetic advantages include rapid and almost complete absorption, minimal insignificant binding to plasma protein, absence of enzyme induction, absence of interactions with other drugs, and partial metabolism outside the liver. The availability of an intravenous preparation is yet another advantage. It has been demonstrated effective as adjunctive therapy for refractory partial-onset seizures, primary generalized tonic-clonic seizures, and myoclonic seizures of juvenile myoclonic epilepsy. In addition, it was found equivalent to controlled release carbamazepine as first-line therapy for partial-onset seizures, both in efficacy and tolerability. Its main adverse effects in randomized adjunctive trials in adults have been somnolence, asthenia, infection, and dizziness. In children, the behavioral adverse effects of hostility and nervousness were also noted. Levetiracetam is an important addition to the treatment of epilepsy.

Keywords: epilepsy, seizures, antiepileptic drugs, long-term therapy, efficacy, safety, levetiracetam

Introduction – long-term management considerations in epilepsy

Epilepsy is a chronic condition characterized by recurrent unprovoked epileptic seizures. Epileptic seizures are the clinical manifestations including symptoms and signs of an abnormal, excessive, and hypersynchronous electrical discharge of neurons in the brain. Thus, a seizure is a symptom. Epilepsy is a condition; it cannot be considered a disease because it can be caused by many etiologies. Epilepsy may be genetic or could be the result of a variety of insults to the brain, including head trauma, stroke, vascular malformations, or congenital brain malformations (Engel 2001). Because seizures and epilepsy are very heterogeneous they have to be classified. The most widely used classification is that proposed by the International League Against Epilepsy in 1981, dividing seizures into those that are partial and those that are generalized (Commission 1981). Partial seizures are ones in which the first clinical and electrographic changes suggest initial activation limited to part of one cerebral hemisphere. Partial seizures are further subdivided into simple partial, complex partial and partial becoming generalized. Simple partial seizures are those in which awareness and responsiveness are completely preserved. Complex partial seizures involve at least an alteration of responsiveness or awareness. Secondarily generalized seizures can start either as simple partial or complex partial, but then spread to the whole brain and most often manifest towards their later part with generalized tonic and then clonic activity. Generalized seizures are those in which the first clinical changes indicate initial involvement of both hemispheres. Consciousness is usually impaired at onset, except for myoclonic

Correspondence: Bassel Abou-Khalil
Vanderbilt University Department of Neurology, A-0118 Medical Center North, Nashville, TN 37232-2551, USA
Tel +1 615 936 0060
Fax +1 615 936 0223
Email bassel.abou-khalil@vanderbilt.edu

seizures which are too brief for altered consciousness to be appreciated. Motor manifestations are bilateral if they occur. The initial electrographic ictal patterns are bilateral. Generalized seizure types include generalized absence, generalized myoclonic, generalized tonic, generalized clonic, generalized tonic clonic, and generalized atonic seizures.

In addition to the classification of epileptic seizures, the International League Against Epilepsy proposed a classification of epilepsies and epileptic syndromes (Commission 1981, 1989). Since most patients have either partial seizure types or generalized seizure types, the two main subdivisions in the classification are partial (focal, local, or localization-related) epilepsies, and generalized epilepsies. Each of these major categories is sub-classified into those epilepsies that are idiopathic and presumed genetic or symptomatic/cryptogenic (probably symptomatic), related to a brain insult. In general, idiopathic epilepsies respond better to treatment than symptomatic epilepsies. Within this epilepsy classification are epileptic syndromes that are characterized by a specific range of age at onset, specific seizure types, specific natural history or course, and specific response to treatment. For example, juvenile myoclonic epilepsy is a type of idiopathic generalized epilepsy in which patients have generalized myoclonic seizures, particularly after awakening, generalized tonic clonic seizures (in about 90%), and generalized absence seizures (in about 30% of cases). In this syndrome, the electroencephalogram (EEG) shows generalized 4–6 Hz spike-and-wave discharges in between seizures. These patients respond well to treatment but their epilepsy is a lifelong condition (Renganathan and Delanty 2003). Some forms of epilepsy are known to have a limited course, with remission expected. For example, benign childhood epilepsy with centrotemporal spikes, also called benign rolandic epilepsy, is an epileptic syndrome in which seizures are usually infrequent, easily controlled, and remit at puberty (Wirrell 1998). However, most epilepsies are chronic and require long-term therapy.

The treatment of epilepsy will depend on appropriate classification of the seizure type and the epileptic syndrome, then the choice of an antiepileptic drug (AED) that is most appropriate for the seizure type and epileptic syndrome and also the safest and most appropriate for the patient's particular medical background. The treatment of epilepsy should always begin with monotherapy, using a low initial dose and titrating slowly. Among the more than sixteen marketed antiepileptic drugs approximately one half are older agents marketed before 1980, while the rest were marketed after 1990 (Table 1) (Schachter 2007). The older AEDs were generally approved for marketing and even used as first-line agents without undergoing the rigorous clinical trials now required of the newer antiepileptic drugs. Regulatory approval for the new AEDs is restricted to the specific epilepsy patient populations in whom the drug has demonstrated efficacy and to the specific mode of use in the relevant clinical trial. For example, a new AED will receive approval for first-line monotherapy use only if demonstrated effective as first-line monotherapy in a sound clinical trial. If the new AED is not started as first-line monotherapy, but monotherapy is achieved after removal of an existing AED, then the regulatory approval will be for conversion to monotherapy only. Among the newer AEDs, the vast majority were initially tested and approved for use as adjunctive therapy. Monotherapy trials typically followed later. Such trials have earned several AEDs approval for monotherapy use. However, the regulatory agencies are not uniform in their criteria for approval of AED indications: some agents have been approved for monotherapy in Europe but not in the US.

If seizures continue despite maximum tolerated doses of the first AED, a change in therapy is indicated. Although an alternative monotherapy is usually recommended at this point, there is no scientific evidence to support the strategy of alternative monotherapy over adjunctive therapy (Kwan and Brodie 2000b; Beghi et al 2003). In general, common sense would decree that if the first drug is not tolerated or if it is totally ineffective, alternative monotherapy is the best approach. If the first drug was well tolerated and was at least partially effective, adjunctive therapy could be considered. The choice of first alternative monotherapy or add-on therapy depends on several factors, including safety, tolerability, efficacy in clinical trials, ease of use, potential for rapid titration, pharmacokinetic interactions, efficacy in co-morbidities, and less prominently mechanism of action. If adjunctive therapy is chosen, potential interactions between the first and the second AED are important factors in the choice of AED (Patsalos and Perucca 2003). Patients who fail a second AED are much less likely to become seizure free with the third next AED than those who have failed only one AED (Kwan and Brodie 2000a). After failure of two or three AEDs, patients with partial epilepsy should be considered for epilepsy surgery, which is highly effective in certain "surgically remediable" epileptic syndromes such as temporal lobe epilepsy with hippocampal sclerosis or focal epilepsy associated with certain benign brain lesions. Patients who are not excellent candidates for epilepsy surgery can undergo additional AED trials, including AED

Table 1 Spectrum of efficacy of standard (**A**), and new AEDs (**B**). The new AEDs are listed in the order of their marketing in the US, following approval by the US Food and Drug Administration

		Partial	1ary GTC	G myoclonic	G absence
A	Phenytoin	+	+	-	-
	Carbamazepine	+	+	-	-
	Valproate	+	+	+	+
	Phenobarbital	+	+	-	-
	Primidone	+	+	+	-
	Ethosuximide	-	-	-	+
	Methsuximide	+	?	?	+
	Clonazepam	+	+	+	+
B	Felbamate	+[b]	+	?	?
	Gabapentin[a]	+[b]	-	-	-
	Lamotrigine[a]	+[b]	+[b]	?	+[b]
	Topiramate[a]	+[b]	+[b]	?	?
	Tiagabine	+[b]	?	-	-
	Oxcarbazepine[a]	+[b]	+?	-	-
	Levetiracetam[a]	+[*]	+[b]	+[b]	?
	Zonisamide	+[b]	+	+	?
	Pregabalin	+[b]	?	-	-

[a]New AED with positive initial monotherapy trials.
[b]New AED efficacy indication supported by blinded trials.

combinations. In general it is advisable to avoid combinations of more than three AEDs because of the risk of interactions and additive adverse effects. Non-pharmacological therapies such as vagus nerve stimulation and the ketogenic diet or modified Atkins diet can also be considered in patients who fail to respond to or are unable to tolerate antiepileptic drugs. However, vagus nerve stimulation is unlikely to produce seizure freedom, and compliance with the ketogenic or Atkins diet can be a major challenge.

Even though the landmark study of Kwan and Brodie suggested that the chances of seizure freedom with a new AED decrease with the failure of each additional AED, one survey of patients who failed epilepsy surgery evaluation found that 21% had achieved seizure remission at follow up, most often due to the addition of one of the new AEDs (Selwa et al 2003). Levetiracetam, the focus of this review is one of these new AEDs.

Levetiracetam

Levetiracetam (LEV) is one of the newest AEDs, marketed worldwide only since 2000. It was initially approved in the US only as adjunctive therapy for partial-onset seizures. However, more recent trials earned it approval as adjunctive therapy for primary generalized tonic-clonic seizures and myoclonic seizures of juvenile myoclonic epilepsy, and a recent comparative monotherapy trial earned it approval for use as initial monotherapy in the European Union, though not in the US. In addition, the recent approval and marketing of an intravenous preparation has added to the versatility of this AED.

Levetiracetam pharmacology

LEV is rapidly and almost completely absorbed after oral intake, with peak plasma concentrations approximately one hour after oral administration. Food reduces the peak plasma concentration by 20% and delays it by 1.5 hours, but does not reduce LEV bioavailability (Patsalos 2000, 2003). There is a linear relationship between LEV dose and LEV serum level over a dose range of 500–5000 mg (Radtke 2001). LEV protein binding, at less than 10%, is not clinically relevant. LEV metabolism is not dependent on the liver cytochrome P450 enzyme system. LEV is predominantly excreted unchanged through the kidneys, with only about 27% metabolized. The main metabolic pathway is hydrolysis of the acetamide group in the blood (Radtke 2001). The resultant metabolite generated is inactive. LEV plasma half-life is 7 ± 1 hours in adults, but can be prolonged by an average of 2.5 hours in the elderly, most likely due to decreased creatinine clearance with age (French 2001; Hirsch et al 2007). In patients with impaired renal function, a dose adjustment is needed, dependent on the creatinine clearance (French 2001). The absence of hepatic metabolism and of protein binding predict absence of pharmacokinetic interactions (Nicolas et al 1999). Indeed, no pharmacokinetic interactions were observed with phenytoin, warfarin, digoxin, or oral contraceptives (Browne et al 2000; Levy et al 2001; Patsalos 2000, 2003;

Ragueneau-Majlessi et al 2001, 2002; Abou-Khalil et al 2003; Coupez et al 2003). However, some studies have suggested lower LEV levels or higher LEV clearance in patients taking enzyme-inducing AEDs (May et al 2003; Perucca et al 2003; Hirsch et al 2007). Autoinduction probably does not occur with LEV, but one study involving short intensive monitoring suggested a drop in serum levels after the fifth day of administration (Stefan et al 2006).

Intravenous levetiracetam

The intravenous formulation of LEV was demonstrated bioequivalent to the oral formulation (Ramael et al 2006b). In the initial study 1,500 mg of LEV were injected over 15 minutes (Ramael et al 2006b). The infusion was well tolerated and adverse effects were similar to those with oral LEV, though somnolence was more common with the intravenous administration. In a second study, higher doses and faster infusion rates were used (2,000, 3,000, and 4,000 mg over 15 min; 1,500, 2,000, and 2,500 mg over 5 min) (Ramael et al 2006a). The most common adverse experiences, dizziness and somnolence, were not clearly related to dose or infusion rate. As expected, the peak plasma level was reached at 5 or 15 minutes, corresponding to the end of the infusion, but otherwise the pharmacokinetic profile was similar to that of oral LEV. LEV infusion over 15 minutes was demonstrated to be a practical alternative in epilepsy patients unable to take the oral medication (Baulac et al 2007).

Pharmacology in children, infants, and neonates

Pharmacokinetics in children were studied in 15 boys and nine girls 6–12 years old who received a single dose of LEV, 20 mg/kg as an adjunct to their stable regimen of a single concomitant AED (Pellock et al 2001). The half-life was 6 ± 1.1 hours. The C-max and area under the curve were lower in children than in adults and renal clearance was higher. The apparent body clearance was 1.43 ± 0.36 mL/min/kg, 30%–40% higher in children than in adults. In another study in younger children and infants, the same dose/Kg was administered as a 10% oral solution to thirteen subjects aged 2.3–46.2 months. The mean half-life was 5.3 ± 1.3 hours in this younger group (Glauser et al 2007). The half-life is likely longer in neonates. Two studies estimated LEV half-life in the neonate at 18 hours (Allegaert et al 2006; Tomson et al 2007).

Pharmacokinetics during pregnancy

Maternal plasma concentrations measured during the third trimester were compared to a "baseline" before pregnancy or after delivery in two small studies (Tomson et al 2007; Westin et al 2008). Both studies found plasma concentrations to be significantly lower during the third trimester in comparison with baseline. The mean concentration-to-dose ratio in the third trimester was 50%–30% of that at baseline. This suggested that the elimination of LEV may be enhanced during pregnancy. However, there was great variability between patients, such that the change in serum concentration could not be accurately predicted.

Serum levels

LEV has linear kinetics, such that in any individual the serum concentration is proportional to the dose (Patsalos 2004). However, the effective serum level for LEV is not known. One study in 69 patients taking 500–3000 mg/day found that the trough plasma concentration ranged from 1.1 to 33.5 μg/mL (Lancelin et al 2007). Similar mean concentrations were found in patients experiencing adverse effects and those without adverse effects (11.2 vs 10.9 μg/mL). The mean plasma concentrations in responders and non-responders were 12.9 and 9.5 μg/mL. The difference was not significant, but the authors suggested that 11 μg/mL could be a threshold concentration for a therapeutic response. The vast majority of patients in this study had refractory epilepsy, making it difficult to study the effective plasma concentration of LEV. Such a study is best conducted in patients with new onset epilepsy. A trial comparing LEV and carbamazepine in newly diagnosed patients did not report plasma concentrations (Brodie et al 2007). However, it found that most patients were seizure-free at the lowest LEV dose of 1000 mg/day. In the therapeutic drug monitoring study mentioned earlier, a daily dose of 1000 mg/day was associated with a mean trough level of 6.5 ± 2.4 μg/mL (Lancelin et al 2007). Even though a therapeutic and toxic LEV concentration are not defined, measuring the serum concentration is helpful to assess compliance. In addition, if a baseline serum concentration is obtained during a period of good seizure control, the serum concentration can be repeated with breakthrough seizures to assess if a drop in concentration played a role. Finally, monitoring serum concentration through the course of pregnancy can help with calculating the recommended dose adjustments needed to correct for increased clearance.

Putative mechanism of action

LEV is different in its mechanism from that of other AEDs, because it is not effective in the standard animal models used to screen for anticonvulsant activity, while it is effective in the chronic kindling model (Loscher and Honack 1993; Klitgaard et al 1998). It was recently established that the

most relevant LEV mechanism of action is through binding to the synaptic vesicle protein SV2A (Lynch et al 2004). The SV2A binding affinity of LEV derivatives correlated strongly with their binding affinity in the brain, as well as with their ability to protect against seizures in the audiogenic mouse model (Lynch et al 2004). Similar findings were noted in the mouse corneal kindling model and the GAERS rat model of generalized absence epilepsy (Kaminski et al 2008). The specific effect of LEV binding to SV2A appears to be a reduction in the rate of vesicle release (Yang et al 2007). LEV has other mechanisms of action that likely play a comparatively smaller role: reversing the inhibition of neuronal GABA- and glycine-gated currents by the negative allosteric modulators zinc and ß-carbolines (Rigo et al 2002), and partial depression of the N calcium current (Niespodziany et al 2001; Lukyanetz et al 2002). At present, the mechanisms of action have not yet helped identify a specific clinical efficacy profile for LEV.

Levetiracetam efficacy – pivotal double-blinded randomized controlled trials

Adjunctive therapy in refractory partial epilepsy in adults

LEV was found efficacious in 3 pivotal placebo-controlled randomized blinded clinical trials in adults with refractory partial epilepsy. These trials investigated three doses, 1000, 2000, and 3000 mg/day. All three doses were found to be effective. The US trial compared 1000 mg/day and 3000 mg/day (in two divided doses) with placebo (Cereghino et al 2000). The study randomized 294 patients, 268 of whom completed the 14 weeks of treatment. After a 12-week single-blind baseline, LEV was titrated over 4 weeks. Patients in the 1000 mg/day group first received 333 mg/day for 2 weeks, then 666 mg/day for 2 weeks, while patients in the 3000 mg/day group received 1000 mg/day for 2 weeks and then 2000 mg/day for 2 weeks. The median percentage reduction in seizures over baseline was 32.5% for LEV 1000 mg/day and 37.1% for LEV 3000 mg/day as compared with 6.8% for placebo. The 50% responder rates were 33% for 1000 mg/day and 39.8% for 3000 mg/day, compared with 10.8% for placebo. Seizure freedom was noted in 3% of patients in the 1000 mg group and 8% of the 3000 mg group. No patients were seizure-free in the placebo group. Maximum efficacy was already present in the first visit 2 weeks after initiating titration.

The European placebo-controlled randomized double-blind trial compared 2000 mg/day, 1000 mg/day, and placebo as add-on treatment (Shorvon et al 2000). Patients randomized to 2000 mg/day received 500 mg bid for 2 weeks, then 1000 mg bid while patients randomized to 1000 mg/day received placebo for 2 weeks, then 500 mg bid. The 4-week titration period was followed by a 12-week maintenance phase. Out of 324 randomized patients, 278 completed the study. There was a 26.5% median seizure reduction from baseline for the 2000 mg/day group, 17.7% for the 1000 mg/day group, and 6.1% for the placebo group. The 50% responder rate was 31.6% for the 2000 mg/day group, 22.8% for the 1000 mg/day group, and 10.4% for the placebo group. Two percent of the 2000 mg patients, 5% of the 1000 mg patients, and 1% of the 112 mg placebo patients were seizure free. In both the US and European trials, both doses tested were more efficacious than the placebo, but were not significantly different from each other.

A third pivotal trial, also conducted in Europe, only compared 3000 mg per day to a placebo (Ben-Menachem and Falter 2000). After the baseline phase, patients randomized to LEV received 1000 mg/day for 2 weeks, then 2000 mg/day for 2 weeks before receiving 3000 mg/day for the remainder of the trial. The median reduction in seizure frequency from baseline was 39.9% for LEV compared with 7.2% for placebo. The responder rate was 50% for LEV compared with 16.7% for placebo. Seizure freedom was reported in 8.2% of LEV patients compared with 1% of placebo patients.

The findings from the above trials were confirmed in a smaller blinded trial (94 patients) conducted in Taiwan, comparing adjunctive 2000 mg/day of LEV to placebo (Tsai et al 2006). The responder rate in the LEV group was 53.5% compared with 10.6% in the placebo group. Seizure freedom was observed in 8.7% of LEV patients, but none of the placebo patients.

The three main pivotal trials received a number of post hoc analyses. Two of these analyses addressed the latency for onset of action of LEV. In one study, it was found that the increase in proportion of seizure-free patients over baseline was 15% for the first day of treatment and 17% for second and third days of treatment for 1000 mg/day, all statistically significant (French and Arrigo 2005). However the increases for 333 mg/day were 7% for Day 1 and 9% for the second and third days. These were not significant. There were no major changes in the placebo group. In a second analysis, the mean proportion of seizure-free days were as computed during each week after initiation of treatment (French et al 2005). The mean proportion of seizure-free days was greater in the LEV than the placebo group and the difference was observed as early as the first week after initiation of treatment. Interestingly, it was also greatest at that point in time, after which it dropped but remained fairly stable. A similar

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