Epilepsy

A new antiepileptic drug

S D Shorvon, K van Rijckevorsel

Levetiracetam, a pyrrolidone recently licensed as an antiepileptic drug

Recently a new antiepileptic drug, levetiracetam (LEV), was approved for the add on treatment of partial epilepsy, both in the United States and in Europe. This is of potential importance, because this drug is from a class not previously used in epilepsy, although piracetam, a compound with a structure similar to that of levetiracetam, is useful in myoclonus. Both drugs are pyrrolidone derivatives, a class of drugs of interest for both psychotropic and nootropic applications and potentially as neuroprotectants. Levetiracetam (available under the registered trademark of UCB S.A., Keppra®) is the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide (fig 1). Homologues sharing the S configuration include a range of other compounds, some of which also have antiepileptic action.[1] The range and extent of the compounds' activity in experimental models of epilepsy and other conditions varies considerably with minor changes to chemical structure, but the full extent of the range of properties of these drugs in humans has not been explored. This article reviews the experimental and clinical data relating to the antiepileptic action of levetiracetam.

EXPERIMENTAL STUDIES

Levetiracetam shows an unusual profile of antiepileptic activity in experimental animal models of partial and generalised epilepsy.[2] Unlike other antiepileptic drugs, levetiracetam has no effect on tonic seizures induced by maximal electroshock or clonic seizures induced by pentylenetetrazol (PTZ) stimulation in the classic rodent models.[2–4] It however has very marked protection against seizures in audiogenic mice, mice kindled with corneal electroshock or PTZ, and amygdaloid kindled rats. It protects against spontaneous spike and wave discharges in the GAERS model and in pilocarpine or kainic acid induced focal seizures in rats.[2 4 5] The dose dependent ability of levetiracetam to inhibit the development of kindling suggests a potential antiepileptogenic effect as well.[6] Levetiracetam is the most effective of any of the pyrrolidone drugs in these epilepsy models. Its R-enantiomer has no antiepileptic activity.

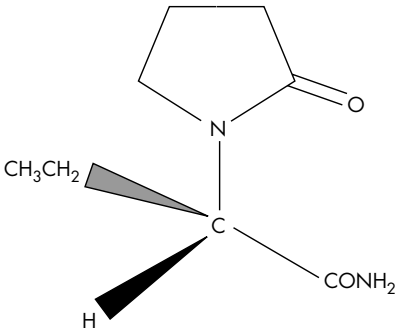

Figure 1 Levetiracetam is a pyrrolidone derivative and is chemically designated (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide. It has a molecular weight of 170.21 and molecular formula of $C_8H_{14}N_2O_2$.

The dose at which toxic effects on the rotarod test are produced is much higher than the effective antiseizure dose in both the GAERS model and the corneally kindled mice. The safety margin of levetiracetam in these models is much greater than for other drugs. In acute and chronic toxicity studies in animals, levetiracetam shows generally low toxicity. Oral doses up to 5000 mg/kg acutely (maximum tested dose) are not lethal in mice and rats. Levetiracetam has not displayed any teratogenic, mutagenic, or carcinogenic properties.

The mechanism of action of levetiracetam (or indeed the other -acetam drugs) is not clearly understood, and it does not seem to involve any conventional modulation of the three main mechanisms relevant for the action of classic antiepileptic drugs.[7] The drug does not bind to receptors associated with excitatory or inhibitory neurotransmitters (for example, γ-aminobutyric acid (GABA), glutamate, glycine, adenosine), has no effect on sodium or T-type calcium channel function, and does not affect GABA transaminase or glutamic acid decarboxylase (GAD) activity or second messenger systems (cyclic adenosine monophosphate, protein kinase C).[2] By contrast, it has recently been reported that levetiracetam reduces high voltage activated Ca^{2+} currents,[8] reverses inhibition of GABA and glycine gated currents induced by negative allosteric modulators,[9] and effects voltage gated potassium channel conductance,[10] suggesting that its mechanism of action differs from other antiepileptic drugs. Levetiracetam also has a specific stereoselective binding site in the CNS,[1] and cannot be displaced from this site by other classic anticonvulsant drugs (carbamazepine, phenytoin, valproate, phenobarbital), although ethosuximide does show binding affinity. The extent of the antiepileptic efficacy in the audiogenic seizure model in mice was found to be correlated with the affinity for the binding site of a series of S-homologues of levetiracetam. Levetiracetam has no binding to membranes outside of the CNS.

CLINICAL PHARMACOKINETICS

The pharmacokinetic properties of levetiracetam have been studied in healthy adult volunteers, patients with epilepsy, and special populations, including paediatric and elderly patients and patients with renal or hepatic insufficiency. Levetiracetam is rapidly and almost completely absorbed after oral administration of doses ranging from 250 mg to 5000 mg, with peak plasma concentrations achieved in about 1 hour and steady state concentrations achieved in 48 hours. Absolute oral bioavailability is nearly 100%. When taken with food, the extent of absorption is not affected, although the rate of absorption may be slowed. Levetiracetam is not significantly bound to plasma proteins (<10%), and its volume of distribution is about 0.6 l/kg, similar to the volume of distribution of intracellular and extracellular water. In addition, levetiracetam exhibits linear, dose proportional, kinetics, with low intrasubject and intersubject variability, and a half life of 6 to 8 hours.[11] Levetiracetam does not undergo hepatic metabolism, nor does it induce or inhibit cytochrome *P*-450 enzymes.[12] Levetiracetam is to a limited extent metabolised (by hydrolysis) by a serine esterase enzyme in blood and other tissues and excreted through the kidneys unchanged or as inactive metabolites.[11]

Renal clearance of levetiracetam is directly proportional to creatinine clearance. Clearance of levetiracetam is significantly reduced in patients with severe hepatic impairment and concomitant renal impairment (hepatorenal syndrome). No differences are seen in patients with mild to moderate hepatic impairment. In studies with elderly patients, the elimination half life of levetiracetam is prolonged to 10 to 11

Abbreviations: LEV, levetiracetam; PTZ, pentylenetetrazol; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; SUDEP, sudden and unexplained death in epilepsy

Table 1 Pooled responder rates for those patients who completed titration and were evaluated on a stable dose (evaluation period), and for all patients randomised (the intent to treat population) during the complete treatment period

	Evaluation period on stable dose				Intent to treat population, total treatment period titration included			
		Levetiracetam				Levetiracetam		
	Placebo (n=301)	1000 mg/day (n=195)	2000 mg/day (n=95)	3000 mg/day (n=269)	Placebo (n=312)	1000 mg/day (n=204)	2000 mg/day (n=106)	3000 mg/day (n=282)
≥50% responder rate	12.6	27.7	31.6	41.3	9.4	28.6	35.2	39.5
≥75% responder rate	3.3	11.8	16.8	22.3	2.6	10.8	16.2	22.4
Seizure freedom*	0.6	3.9	2.1	8.2	0.3	2.9	2.8	6.0

*Seizure-free during the analysed period (evaluation period or total treatment period).

hours and is likely attributable to the age related decline in renal function. After single oral dose administration of 20 mg/kg levetiracetam in children between 6 and 12 years old, total body clearance was about 30% to 40% higher than in adults, and the half life was roughly 6 hours.[13]

Because it does not undergo hepatic metabolism and is not significantly protein bound, levetiracetam has a very low potential for pharmacokinetic interactions. Findings from studies in vitro,[12] clinical trials in patients,[14–16] and specific studies with digoxin,[17] phenytoin,[18] warfarin, valproic acid, and oral contraceptives[11] support this assertion.

CLINICAL ANTIEPILEPTIC EFFECT

Add on therapy in partial epilepsy

The efficacy of levetiracetam as add on therapy has been assessed in three prospective, double blind, placebo controlled trials in patients with refractory epilepsy. The studies were powered for parallel group comparison.[14–16] Doses of levetiracetam evaluated in these trials included 1000, 2000, and 3000 mg/day given in twice daily regimens. A total of 904 patients with refractory partial seizures, with or without secondary generalisation, who were not controlled despite being on a stable dose regimen of one to a maximum of two marketed antiepileptic drugs, participated in these trials. Patients were evaluated after 12 or 14 weeks, and seizure frequency during the evaluation period was compared with a baseline period of 8 or 12 weeks. Demographic characteristics across studies were comparable for sex, age, race, and other baseline assessments. Responder rate and seizure count analyses were based on the patients who completed titration and entered the stable dose evaluation period (n=860). In addition, the responder rates were also analysed for the total randomised population during the treatment period (the intent to treat population; n=904). The data from both analyses are presented in table 1.

At all doses evaluated in these studies, levetiracetam was significantly more effective than placebo. The median percentage reduction from baseline was 32.5 for patients receiving levetiracetam compared with 7 for patients receiving placebo (p<0.001). The responder rate (the proportion of patients experiencing a 50% or greater reduction in seizure frequency compared with baseline) during the evaluation period was 27.7% (54/195), 31.6% (30/95), and 41.3% (111/269) for patients receiving 1000, 2000, and 3000 mg/day respectively, compared with 12.6% (38/301) of patients who received placebo (fig 2; p>0.001, all doses versus placebo). The percentage of patients experiencing a 75% or greater reduction in seizures was 11.8% (23/195), 16.8% (16/95), and 22.3% (60/269) of patients receiving 1000 mg, 2000 mg, and 3000 mg of levetiracetam respectively, compared with 3.3% (10/301) of placebo treated patients (p<0.001, all doses versus placebo). In addition, 5.7% (32/559) of patients treated with levetiracetam became seizure free, compared with 0.6% (2/301) in the placebo group (p<0.001). A statistically significant reduction in seizure frequency for all different subtypes of partial seizures (simple partial, complex partial, and secondarily generalised seizures) was found with levetiracetam treatment (fig 3).

Monotherapy

One of the efficacy trials was extended into a levetiracetam responder selected monotherapy phase.[16] Forty nine of the 69 patients (71%) who were selected for the monotherapy phase were successfully down titrated, and 36 of 69 (52%) completed the monotherapy phase. The median percentage reduction compared with baseline was 73.8% (p=0.037), the 50% responder rate was 59.2% (29/49), and nine patients (18.4%) remained seizure free during monotherapy.

Long term efficacy studies

Long term analysis of results from the 1422 patients with epilepsy from the first day of exposure to levetiracetam or placebo in phase I, II, or III studies show estimated retention rates (Kaplan-Meier analysis) of about 60% after 1 year (number of patients at risk=826), 44% after 2 years (number of patients at risk=489), and 32% after 4 years (number of patients at risk=175), for up to 8 years (number of patients at risk=1).[19] Twenty six per cent of patients withdrew due to reasons inherent to clinical trials, 16% due to adverse events and 18% due to lack of efficacy. Of the patients with a baseline evaluation (n=1321), 548 (41.5%) had≥50% and 355/1321 (26.9%) had≥75% reduction in seizure frequency compared with baseline during the last 6 months of therapy. Of the 1422 patients, 183 (12.9%) were seizure free for at least 6 months, and 109 (7.7%) were seizure free for at least 1 year. The efficacy of levetiracetam was maintained over time. Sixty six (5%) of the patients were successfully converted to monotherapy.

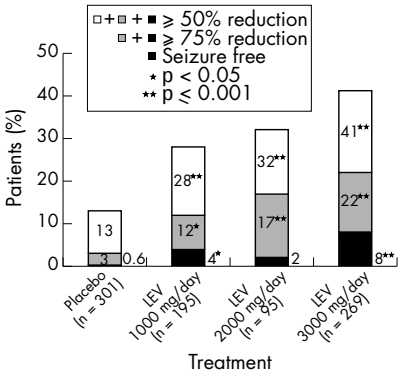

Figure 2 Pooled efficacy results showing the responder rates during the evaluation period at three different doses, and on placebo. LEV=levetiracetam.

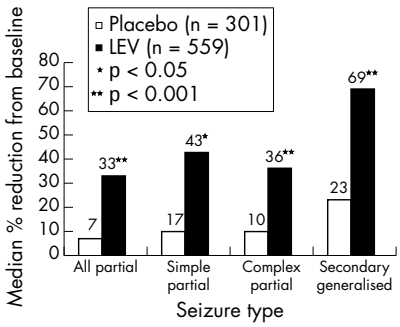

Figure 3 Pooled efficacy results showing the median % reduction from baseline in partial seizure subtypes; LEV=levetiracetam.

Other seizure types

The range of effectiveness of levetiracetam in human epilepsy has not yet been fully explored, but there are some indications that the drug will be useful in a wider range of seizure types and syndromes.[20] Preliminary open studies of levetiracetam in patients with generalised tonic clonic, absence, and myoclonic seizures have been very encouraging, as they have in the multiple seizure types of the Lennox-Gastaut syndrome. The drug also has a dramatic effect on photosensitivity,[21] and there is pilot data suggesting potential effectiveness in refractory juvenile myoclonic epilepsy.[22]

Table 2 Adverse events (%) according to FDA and EMEA standards

	Adverse reaction* (FDA)		Undesirable effects† (EMEA)	
	Levetiracetam (n=769)	Placebo (n=439)	Levetiracetam (n=672)	Placebo (n=351)
Somnolence	15	8	12	9
Asthenia	15	9	7	3
Dizziness	9	4	14	8
Infection	13	8	—	—

*Adverse reaction: any event reported during clinical trial; FDA, Food and Drug Administration; †undesirable effect: all adverse events at least possibly related to the study drug; EMEA=European Medicinal Evaluation Agency.
Note: Adverse reactions and undesirable effects are derived from three efficacy and one safety, double blind placebo controlled trials. Patient numbers differ because the FDA included the crossover part of the study in the analysis, and these patients were counted twice.

SIDE EFFECTS

One of the striking aspects of the clinical trial programme of levetiracetam was the low rate and mild nature of the reported side effects. The incidence of the most common adverse reactions (the FDA term) and the most common undesirable effects (the European Medicinal Evaluation Agency term) derived from three efficacy trials and one safety placebo controlled, double blind trial are shown in table 2.[14–16] The side effects were primarily related to the CNS. Somnolence, asthenia, and dizziness were most commonly reported. In the pooled analysis, there was no evidence of a dose dependent relation within the recommended dose range of 1000 to 3000 mg/day. Patients receiving levetiracetam also reported a slightly higher incidence of symptoms of upper respiratory infection, which was not associated with leukopenia or dose reduction. The proportion of patients who discontinued treatment prematurely or required a dose reduction because of an adverse event was not significantly different between levetiracetam and placebo groups (15.0% *v* 11.6%). Adverse events that led to withdrawal in patients treated with levetiracetam included somnolence (4.4%), convulsion (3.0%), dizziness (1.4%), asthenia (1.3%), and headache (1.0%). A greater percentage of patients from the placebo groups discontinued because of convulsion (3.4%) and rash (1.1%). A worsening of seizure, defined as an increase in seizure frequency of ⩾25%, was significantly lower in patients treated with levetiracetam compared with placebo (levetiracetam, 14.2%; placebo, 25.6%; $p<0.001$). During long term treatment, only 225 (16%) of the 1422 patients withdrew because of an adverse event.[19]

During long term treatment, there was a slightly higher incidence of psychiatric side effects recorded than in the placebo controlled phase and these included irritability, aggression, anger and hostility, and hallucinations. It would be wise to monitor patients for these side effects especially if prone to psychiatric disorders. Throughout the entire clinical development programme, there were 22 deaths of patients with epilepsy receiving levetiracetam (crude mortality rate 0.91 per 100 patient-years). Eight were sudden and unexplained death in epilepsy (SUDEP) in the levetiracetam group (3.54 per 100 person years) versus one in the placebo group (6.58 per 100 person years). The difference was not significant.

Safety data regarding laboratory and physical examinations have been obtained from 3347 patients exposed to levetiracetam (adults with epilepsy, n=1393; children, n=29; patients with other diseases, n=1558; healthy volunteers, n=367), for a total of 2421 patient-years. Overall, physical and neurological examinations were unremarkable in patients treated with the drug. Minor but statistically significant decreases were found in mean values of the red blood cell count, haemoglobin, and packed cell volume, but there were no significant changes in other laboratory parameters.

DOSING RECOMMENDATIONS

The recommended dosing regimen for levetiracetam as add on therapy is twice daily doses of 500 mg to 1500 mg, for a total daily dosage of between 1000 mg and 3000 mg. Higher doses have been studied, but with little evidence of added effectiveness. The initial starting dose of 1000 mg/day has been shown to be clinically effective, but if sufficient seizure control is not obtained, doses can be increased up to 3000 mg/day. In patients with renal impairment, doses should be adjusted downwards in accordance with creatinine clearance.[23 24] At present, sufficient data are not available to recommend treatment with levetiracetam during pregnancy. In patients withdrawn from levetiracetam, a gradual tapering of 1000 mg every 1 to 2 weeks has been successful and has not resulted in withdrawal seizures.

The introduction of a new antiepileptic from a novel class of drug is an interesting development. The remarkable stereospecificity of levetiracetam and the diversity of properties of related compounds are intriguing.[1] The fact that the different pyrrolidone derivatives have such different properties encourages our view that the full range of actions of levetiracetam has not been fully explored. Its usefulness in a wide range of seizure types has been suggested in open label studies and would indicate further clinical investigation, and studies in non-epilepsy indications such as myoclonus, migraine, neuropathic pain, bipolar disease, and other areas could be worthwhile. As an antiepileptic drug, it has a preclinical profile which is unlike any other marketed antiepileptic drug, favourable pharmacokinetics, good efficacy, and an excellent safety profile (at least at this stage of experience), and also a broad spectrum potential. For all these reasons, it is already likely to become an important addition to the range of medications which are currently available for epilepsy.

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Authors' affiliations

S D Shorvon, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK and National Hospital for Neurology and Neurosurgery London, UK, and the National Neuroscience Institute, Singapore
K Van Rijckevorsel, Centre Neurologique William Lennox, Université Catholique de Louvain, Ottignies-Louvain La Neuve, Belgium

Correspondence to: Professor S Shorvon, Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK; s.shorvon@ion.ucl.ac.uk

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EDITORIAL COMMENTARIES

Schizophrenia

Improved antisaccade performance in schizophrenia with risperidone

S B Hutton

Atypical treatment improves cognitive function

Several recent studies have suggested that atypical antipsychotic medications such as risperidone can ameliorate certain cognitive deficits associated with schizophrenia.[1] Such findings have important implications, as cognitive impairment is a significant predictor of both social and occupational functioning in schizophrenia. In this issue, Burke and Reveley (pp 449–454)[2] show that patients treated with the atypical antipsychotic risperidone make fewer antisaccade errors than when they are treated with conventional antipsychotic drugs.

The antisaccade task has a number of advantages over more traditional neuropsychological indices of cognitive function in schizophrenia: it is quick to administer, the instructions are simple to comprehend, and performance can be measured objectively and accurately. Furthermore, antisaccade errors (reflexive saccades towards a sudden onset target, instead of away from it) are thought to reflect dysfunctional inhibitory control processes. Such processes are generally associated with the dorsolateral prefrontal cortex and are particularly impaired in schizophrenia. The author's findings support suggestions that oculomotor paradigms may prove to be a particularly sensitive tool for evaluating the neurocognitive effects of antipsychotic medications.[3]

Recently, increased antisaccade errors have been reported in the first degree relatives of patients with schizophrenia, leading to the suggestion that saccadic disinhibition may be a useful marker of genetic vulnerability to the disorder.[4] The findings of Burke and Reveley suggest that saccadic disinhibition may reflect "state" as well as "trait" factors. This has important implications for the utility of antisaccade error rate as a biological marker for schizophrenia and merits further investigation.

By using a counterbalanced crossover design, in which one group of patients switched from typical antipsychotics to risperidone and another group switched in the opposite direction, Burke and Reveley were able to show that the reduction in antisaccade errors associated with risperidone treatment is not simply the result of practice effects. Given that many of the claims for beneficial effects of atypical antipsychotic medications on cognition are based on less robust methods,[5] this is a considerable contribution. However, it should be noted that the groups studied by Burke and Reveley were small and it is important that their findings are replicated and extended in a larger sample.

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Author's affiliations

S B Hutton, Department of Experimental Psychology, University of Sussex, Falmer, Brighton BN1 9QG, UK

Correspondence to: Dr S B Hutton; samh@biols.susx.ac.uk

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