Levetiracetam in the management of epilepsy

John Paul Leach

Epilepsy is one of the commonest neurological conditions. For historical reasons, this condition is often managed in the UK by non-specialists. Treatment options have increased markedly in the last 15 years, with a resultant increase in the potential for better seizure control and an enhanced quality of life for patients with epilepsy.

Epilepsy is one of the commonest neurological conditions which manifests as a tendency to have repeated unprovoked seizures. Incidence increases at the extremes of life, and among all populations it has a point prevalence of 0.5–1.0% and a cumulative lifetime prevalence approaching 3% (Hauser et al, 1993). Even in developed countries like the UK and the United States, much of the burden of epilepsy care is undertaken by non-specialists, mainly GPs and general physicians (Willmore, 1997). Whatever the care setting, refractory epilepsy remains a significant problem; figures for remission are remarkably consistent, with around 30–40% of all patients failing to become seizure free for a significant length of time (Kwan and Brodie, 2000). Antiepileptic drugs (AEDs) have been effective in stopping seizures, but of no demonstrable use in preventing future seizures happening. In other words, while being effective anticonvulsants, existing AEDs are not definitely antiepileptogenic.

This situation may be changing – the last 15 years have seen a host of new treatments made available. The increased opportunity for effective and well-tolerated medication has led to a significant potential for enhanced quality of life for many patients with epilepsy. In addition, there are theoretical reasons why some newer treatments may have added qualities in prevention of future tendencies towards seizures (but no clinical evidence to support this) (Klitgaard and Pitkanen, 2003). As the use of the newer drugs increases, it becomes increasingly important for GPs and general physicians to be aware of the problems and opportunities afforded by this new generation of treatments. This review concentrates on the latest drug to be introduced, levetiracetam.

Dr John Paul Leach is Consultant Neurologist in the Department of Neurology, Southern General Hospital, Glasgow G51 4TF and Epilepsy Unit, Western Infirmary, Glasgow

HISTORY OF DRUG TREATMENTS FOR EPILEPSY

Serendipitous discoveries in the late 19th and early 20th century led to the widespread use of the two original anticonvulsant compounds, bromide salts and barbiturates. Both treatments had significant side effects, but were unrivalled until the discovery by Merrit and Putnam in 1939 of diphenyl hydantoin, a more selective sodium-channel blocker with fewer sedative properties.

The range of treatments available increased in the 1960s with the introduction of carbamazepine (a modified tricyclic drug), and valproate in 1970s (a short chain fatty acid soluent 'control' substance which transpired to have anticonvulsant properties). As well as their recognized side-effect profiles, the incomplete efficacy and the pharmacological quirks (hepatic enzyme induction, mutual interactions) of these drugs ensured that newer AEDs would be very welcome.

The drive for discovery of newer treatments resulted in a host of new treatments being made available in the UK. The late 1980s saw the introduction of vigabatrin and lamotrigine, the first two new AEDs. These compounds arose from innovative drug development programmes targeting new epileptogenic pathways, and they were soon joined by other novel AEDs (*Table 1*). This article looks at the newest of these drugs, levetiracetam (Keppra, UCB Pharma Ltd, Watford), how it works and how well it works. The article also compares levetiracetam with other AEDs, and looks at the most common side effects and what kinds of patients respond well.

LEVETIRACETAM

Nature

Piracetam, a pyrrolidone derivative, underwent investigation of supposed nootropic properties,

and was known to display efficacy against myoclonus but no other seizure types. Levetiracetam, another pyrrolidone, is chemically unrelated to any other AEDs. These structural differences explain the novel pharmacokinetic and pharmacodynamic properties of levetiracetam.

Mode of action

Levetiracetam has no effects on the recognized antiepileptic mechanisms: excitatory and inhibitory mechanisms are unaffected by levetiracetam, and there has been no demonstrable effect of levetiracetam on ion channel functioning (Noyer et al, 1995). It rapidly became apparent that levetiracetam's mechanism of action was different from those of other established AEDs. A unique binding site specific for levetiracetam has been identified as a protein associated with synaptic vesicles called SV2A which may modify exocytosis (Lynch et al, 2004). The physiological effect of this binding remains unknown.

Pharmacokinetic profile

The pharmacokinetic profile of an ideal AED includes high oral bioavailability, a long half life, low plasma protein binding, no need for metabolic transformation, significant renal elimination, linear kinetics, no active metabolites and lack of drug interactions (Patsalos, 2000).

Levetiracetam fulfils most of these criteria (Patsalos, 2000). Absorbtion following oral administration is almost complete whether or not it is taken with food. The plasma elimination half life of levetiracetam is 6–8 hours. The majority of the drug is excreted unchanged in the urine; two inactive metabolites have been described which are not dependent on the hepatic cytochrome P450 system. This largely renal clearance means that elimination of levetiracetam is linear. The lack of effect of or on hepatic enzyme systems explains the lack of interactions between levetiracetam and other AEDs. Similarly, there are no mutual interactions between levetiracetam and other commonly used drugs such as coumarin anticoagulants or oral contraceptives (Patsalos, 2000). No correlations have been shown between plasma levels and clinical effect, so routine monitoring of plasma levels is unnecessary.

TABLE 1.
Comparison of different antiepileptic drugs

			Adverse events		
Drug	Spectrum of action	Mode of action	Acute idiosyncratic	Chronic toxicity	Teratogenicity
Barbiturates	Tonic clonic seizures	Multiple mechanisms	Rashes	Tolerance, habituation, withdrawal seizures, behavioural change	Confirmed in man and animals
Carbamazepine	Partial epilepsy	Sodium channel blockade plus multiple others	Rashes, low white cell count	None definite	Confirmed in man and animals
Felbamate	Partial/generalized (monotherapy/add-on)	Glycine antagonism	Bone marrow suppression, hepatic failure	Unknown	Unknown
Gabapentin	Partial (add-on)	Uncertain ?GABAergic effect ?Ca channel blockade	Behavioural problems (children)	Unknown	Unknown
Lamotrigine	Partial/generalized (monotherapy/add-on)	Sodium channel blockade	Rash	Unknown	None described as yet
Levetiracetam	Partial/?generalized (add-on/?monotherapy)	Action via specific binding sites	–	Unknown	Unknown
Oxcarbazepine	Partial (add-on)	Na channel block Ca channel block	–	Hyponatraemia	Unknown
Phenytoin	Tonic clonic seizures	Sodium channel blockade plus multiple others	Rashes, lymphadenopathy, hepatitis	Gum swelling, acne, hirsutism, folate deficiency	Confirmed in man and animals
Sodium valproate	Idiopathic generalized + partial epilepsy	GABAergic enhancement plus multiple others	Gastric intolerance, hepatotoxicity (in children)	? Weight gain, alopecia	Confirmed in man and animals
Tiagabine	Partial (add-on)	GABA reuptake block	Partial status	Unknown	Animal models
Topiramate	Partial/?generalized (add-on/monotherapy)	GABAergic Na channel block Kainate receptor block	–	Renal calculi weight loss	Animal models
Vigabatrin	Partial (add-on)	GABA-t inhibition	Psychosis	Visual field defects	Animal models
Zonisamide	Partial/?generalised (add-on/?monotherapy)	Na channel block	–	Renal calculi	Animal models and isolated case reports in humans

GABA = Gamma-aminobutyric acid

CLINICAL USE

Efficacy

Localization-related epilepsy: Two pivotal studies confirmed the efficacy of levetiracetam as add-on therapy in refractory epilepsy at doses between 1000 and 4000 mg per day.

Shorvon et al (2000) conducted a double-blind placebo-controlled study of levetiracetam in the treatment of refractory localization-related epilepsy in 324 patients. Seizure frequency was reduced by both doses of levetiracetam on comparison with placebo: efficacy was noted on all seizure types. Seizures were reduced by at least 50% (the responder rate) in 31.6% of those on levetiracetam 2000 mg/day compared to 10.4% on placebo. Both doses of levetiracetam reduced individual seizure types more often than placebo.

Cereghino et al (2000) conducted a study of similar design comparing the effects of levetiracetam at doses of 1000 and 3000 mg/day with placebo in 268 patients with refractory epilepsy. Total seizure frequency was again reduced by both doses of levetiracetam, responder rate for 1000 and 3000 mg/day being 33.0% and 39.8% respectively compared to 10.8% for placebo. Seizure freedom was attained in 5.5% of patients on levetiracetam compared to 0% of those on placebo.

Combined efficacy analyses: Similarities in design of these studies allowed their results to be pooled for further analysis. This gave data on 592 patients treated with levetiracetam to compare with 312 patients treated with placebo (Leppik et al, 2003). This combined analysis purported to show an even greater effect against secondary generalized tonic–clonic seizures than against partial seizures.

Frequency of different seizure types was reduced by a greater mean percentage with levetiracetam treatment (whatever the dose) compared to placebo. Similarly, mean percentage reduction in frequency of complex partial seizures was significantly greater with levetiracetam than placebo. As with other AEDs, this effect was most marked with generalized seizures (68.4% *vs* 22.6%). Responder rates (percentage achieving at least 50% reduction in seizure frequency) and seizure freedom rates were significantly higher with levetiracetam treatment than placebo. These differences were present when data were analysed individually for complex partial and secondarily generalized seizures, but not for simple partial seizures.

Generalized epilepsies: Levetiracetam has been shown to be effective in animal models of generalized epilepsies. A retrospective review of 13 patients treated with levetiracetam as open label add-on for refractory juvenile myoclonic epilepsy (Smith et al, 2000) showed that 54% became seizure free while the responder rate was 92%. This efficacy was noted against both generalized tonic–clonic seizures and myoclonic jerks. The period of follow up for each patient was at least 1 year, and patients were receiving an average of three baseline AEDs.

Of 55 patients with different idiopathic generalized epilepsies from three centres in the UK and the USA (Krauss et al, 2003), 76% had a significant reduction in seizure frequency, with 40% of treated patients becoming seizure free. A cohort of 36 patients with generalized epilepsies (Krauss et al, 2001) were followed up as part of an open study at Johns Hopkins University. Efficacy data were similar to the multicentre open study mentioned above. Levetiracetam treatment caused 42% to become seizure free, while a significant (>50%) reduction in seizure frequency was achieved in 75%. Dose range was anywhere between 500 and 4000 mg/day, with a mean daily dose of 1620 mg being administered.

Betts et al (2000) demonstrated a percentage reduction in seizure frequency of 47–67% at doses of 2000–4000 mg/day among 32 patients with generalized epilepsy (placebo 6%), while open label administration to 38 patients with generalized epilepsy elicited a median reduction in seizure frequency of 68%.

While full double-blind trials of levetiracetam in generalized epilepsies are awaited, there is enough early evidence to confirm that levetiracetam has a broad enough spectrum of action to allow its use in generalized as well as localization-related epilepsies. Double-blind studies examining the effects of levetiracetam in juvenile myoclonic epilepsy are underway.

Tolerability

Adverse effects: The adverse event profile of levetiracetam compares very favourably with other AEDs (Arroyo and Crawford, 2003). Withdrawal from levetiracetam (or dose reduction) as a result of adverse events experienced occurred in 15% of those treated in double-blind studies compared to a withdrawal rate of 11% from placebo. The majority of adverse events were mild or moderate in severity, and all were reversible. The most common adverse events noted with levetiracetam are somnolence, asthenia and dizziness (Arroyo and Crawford, 2003). Around 14% of patients had their seizure frequency significantly increased (by at least 25%); this compared with seizure exacerbations in 26% of those on placebo.

Long-term studies using open-label levetiracetam in 1422 patients for up to 5 years showed a

withdrawal rate of around 16%: withdrawals were most commonly the result of seizure worsening (3.4%), somnolence (2.0%), asthenia (6%), depression (6%), dizziness (0.5%) and headache (0.5%) (Krakow et al, 2001).

POST MARKETING SURVEILLANCE OF LEVETIRACETAM

While randomized trials are important in proving efficacy and tolerability, there is a role for unblinded retrospective studies which can demonstrate experience where the dose and concomitant medications can be changed as necessarily. Four such studies have been published.

Betts et al (2003) reviewed the records of 120 patients with levetiracetam treatment for at least 1 year. Seventy seven per cent of patients remained on levetiracetam at the end of 1 year, with 32% and 26% of patients being seizure free after 6 months and 1 year respectively.

Bird and Joseph (2003) examined efficacy outcomes in 175 patients on levetiracetam, 30% of whom had severe or profound learning difficulties (the incidence of learning difficulties denotes a likelihood of more refractory nature of epilepsy). A reduction in seizure frequency of at least 50% was seen in 72% of patients, with 14% being seizure free.

Nicolson et al (2004) found a high retention rate among 245 patients on levetiracetam for up to 2 years. Forty nine per cent exhibited some improvement in seizure frequency, while withdrawal as a result of side effects was 14%. This compared very favourably with withdrawal rates from other AEDs.

Mohanraj et al (2004) followed up 156 patients with various epilepsy types. Seizure freedom was attained in 26%, with a further 21% having seizure frequency at least halved. Twenty four per cent required withdrawal at least in part as a result of adverse events.

EXPANDING CONDITIONS OF USE

Levetiracetam as monotherapy

Levetiracetam has a licence for use as add-on therapy, but evidence is beginning to accrue that levetiracetam could be a useful AED monotherapy. The first such evidence of effect of levetiracetam as monotherapy came from extension of the European double blind study (Ben Menachem et al, 2000); patients who had a significant response to add-on therapy were given the option of having their baseline medication withdrawn. Of 69 patients responding to levetiracetam, 49 (71%) successfully converted to monotherapy, which was significantly more than the numbers converting to placebo monotherapy. The median percentage reduction in partial seizure frequency was 73.8% of baseline frequency with levetiracetam treatment.

Retrospective review was carried out on 14 monotherapy-treated elderly patients with localization-related epilepsy (Alsaadi et al, 2004). Five patients had levetiracetam started as first line, and nine had withdrawn to monotherapy. Thirteen patients received levetiracetam for longer than 6 months, of whom eight (61.5%) became seizure free. Four other patients had a reduction in seizure frequency by more than 50%, giving a response rate in this group of 92%. Only one patient had no significant change in seizure frequency after starting levetiracetam. Dosages used to control seizures ranged from 500 to 3000 mg/day (mean 1839.2 mg/day).

Further definitive studies are underway to examine the use of levetiracetam monotherapy in order to justify further licence extensions.

COMPARISON WITH OTHER AEDS: META-ANALYSIS

The efficacy of levetiracetam has been examined as part a Cochrane systematic review. A meta-analysis of four studies (Chaisewikul et al, 2004) has confirmed a significant advantage over placebo, with an overall odds ratio (OR) for 50% or greater reduction in seizure frequency outcome of 3.81 (with 95% confidence interval (CI) 2.78–5.22). The OR for requiring drug withdrawal, in contrast, was not significantly greater than placebo with an OR of 1.25 (95% CI 0.87–1.80), suggesting that the efficacy of levetiracetam is disproportionately greater than its propensity to cause adverse events. Quality of life and cognitive effect outcomes suggest that levetiracetam has a positive effect on cognition and some aspects of quality of life. Both these outcome measures compare favourably with other AEDs (Marson et al, 2001).

The number of patients needed to treat (NNT) with levetiracetam to obtain a case of at least 50% reduction in seizure frequency is sometimes calculated to give a measure of efficacy. The NNT for levetiracetam is 3.92, implying that seizure frequency will be at least halved in one person for every four patients started on levetiracetam (Van Rijckevorsel, 2001). This measure is comparable with the best of the newer anticonvulsants (Cramer et al, 2001).

Future use of levetiracetam

Use of levetiracetam has been described in animal models or human cases of anxiety syndromes, movement disorders, stiff man syndrome, spasticity and neuropathic pain.

Whether a license will be gained for any of these indications is uncertain, but they remain promising avenues for drug development.

Future of antiepileptic drug treatment

Over the last 150 years, the story of AED use has been one of progression by degrees. Initial treatments have proven useful in generalized seizures, but were beset by severe side effects. Successive generations have given rise to further increments in seizure control, largely as a result of the improved tolerability.

Levetiracetam is the latest of the new generations of AED to be given a licence in the UK, and is confirmed as a potent AED with a very favourable tolerability profile. Levetiracetam use will increase as other license extensions are granted to include other epilepsy types and use as monotherapy. Such increases will be aided by the proven efficacy, ease of use, and lack of resultant pharmacokinetic and pharmacodynamic difficulties. **HM**

Conflict of interest: Dr Leach has spoken at meetings sponsored by manufacturers of all new antiepileptic drugs.

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KEY POINTS

- Treatment options for epilepsy are expanding.
- The major benefit of newer drugs lies in their tolerability.
- Use of the newer drugs as polypharmacy is easier because of their simpler linear kinetics and lack of interactions.

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