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Levetiracetam and behavioural problems in children

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Levetiracetam, a new antiepileptic drug with a novel mechanism of action, was introduced to the market in the year 2000. Pre-clinical studies suggested good tolerability. However, more recent reports have highlighted neurobehavioural side effects associated with the drug, both in adults and in children. In this article we outline the behavioural problems which have been described with levetiracetam use in children, and explore the risk factors potentially associated with such side effects. We illustrate the concept of behavioural side effects with levetiracetam using the case of a child from our own practice.

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Introduction

Epilepsy remains the most common serious neurological disorder worldwide and is a challenging neurological disorder in children. Long term administration of antiepileptic drugs alone or in combination remains the best approach to epilepsy treatment[1]. However, approximately 25–30% of children with epilepsy experience treatment resistant seizures or significant side effects limiting the use of existing antiepileptic drugs[2].

Advances in neurobiology, molecular biology and pharmaceutical science have led to the development of a number of new antiepileptic drugs in the past decade, offering potential advantages in terms of less variable kinetics, lower drug interaction potential[1], and better tolerability[3,4].

Levetiracetam (LEV), one of the "new" antiepileptic drugs, has a novel mechanism of action, a good pharmacokinetic profile and minimal drug-drug interactions. Although LEV has been available since 2000, the full side effects profile is still being determined, especially in children under the age of 16, for whom it is not currently licensed[5]. Pre-marketing clinical trials showed good tolerability[3,6]. However, recent studies and reports have indicated a higher prevalence of neurobehavioural side effects than previously realised[2,7-9].

Pharmacology of levetiracetam

LEV [(-)-(s)-α-ethyl-2-oxo-1-pyrrolidine acetamide], a pyrrolidine derivative, is one of the most recently licensed antiepileptic drugs. It was approved in the US in November 1999 and in Europe in September 2000 as adjunctive therapy for partial seizures in patients over 16 years[10]. Antiepileptic activity is not detected in routinely used seizure models, suggesting a novel mode of action[1,11,12]. LEV binds to synaptic vesicle protein SV2A on plasma membranes of CNS neurons[12], markedly suppresses kindling development, and

inhibits neuronal hypersynchronisation when epileptic activity is evoked[13]. However, the exact mechanism of action of LEV is uncertain. Reduction of repetitive action potential generation may be partially explained by reduction in delayed rectifier voltage operated potassium channels[14]. Action may also entail blockage of zinc and beta carbolines to prevent them from interrupting chloride influx in the γ-aminobutyric acid (GABA) and glycine receptors[4,5].

LEV comes close to fulfilling desirable pharmacokinetic characteristics for an antiepileptic drug. It has high oral bioavailability, unaffected by food, and is absorbed completely and rapidly from the gastrointestinal tract with peak plasma concentration reached in one hour, and steady state within 48 hours. The half life is 6-8 hours in adults and 6 hours in children[15], but the duration of clinical action allows for twice daily dosing[16]. It is not significantly bound to plasma proteins (<10%). It is eliminated partly in the unchanged form by the kidneys (66%), and partly by hydrolysis of the acetamide group to an inactive carboxylic metabolite[15]. Its metabolism does not involve any significant oxidation by the microsomal mixed function oxidases, and it is not vulnerable to a clinically significant degree to inducers or inhibitors of oxidative drug metabolism[3]. The decreased propensity towards drug- drug interactions is advantageous as partial seizures sometimes require a combination of antiepileptic drugs for control[16].

Clinical trials with levetiracetam

In several clinical trials with LEV in adults with epilepsy, a total of 1422 patients were exposed, the drug was generally well tolerated and the predominant side effects were somnolence, dizziness and asthenia, mostly within the first month of treatment[7]. It led to an overall improvement in epilepsy related quality of life[10]. In initial clinical trials (placebo controlled) in adults LEV was deemed to be one of the drugs with a low profile of behavioural side effects.

There have been no systematic trials in children, only smaller studies and case reports. In an open label trial of LEV as adjunctive therapy in 22 paediatric subjects with resistant partial seizures, baseline seizure frequency was compared to that after 14 weeks of LEV therapy[17]. 52% of subjects had more than a 50% decrease in seizure frequency. The drug was especially effective in reducing secondary generalisation of seizures, but worked well in all seizure subtypes. The adverse drug effects were mostly minor: somnolence, upper respiratory tract infections (but no effect on white cell count), headache and anorexia. There was no specific mention of behavioural side effects[14]. The dose was increased from 10 mg/kg/day to 40 mg/kg/day over 4 weeks[2].

Neurobehavioural side effects

Despite the original perception of LEV as being well tolerated[6], in the post-marketing phase reports about behavioural dysfunction in both adults and children came to attention.

In response to reports of behavioural side effects, behavioural symptoms were analysed from the LEV database of the original pre-marketing placebo controlled epilepsy trials in adults[6,7]. Behavioural side effects were reported as occurring in 13% of patients on LEV, compared to 6.2% in the placebo group ($P<0.001$)[6]. Side effects reported included anxiety, apathy, emotional lability, antisocial behaviour, depression, euphoria, hostility, neurosis, personality disorder and depersonalisation. Variables associated with behavioural side effects were a previous psychiatric history, a history of generalised seizures and status epilepticus, febrile convulsions and a faster titration to maximum dose[8,9].

An extensive search of Embase and Medline (1996-December 2004) retrieved only one article describing behavioural effects in children on LEV[5]. The article describes four cases of children or adolescents who developed psychosis within three months of initiating LEV[5]. All four children had dramatic improvement within days of either discontinuing or decreasing the dose of LEV. We describe a similar case in the case report below.

Case report

A 7 year old girl with a longstanding history of tonic clonic and complex partial seizures presented with aggressive behaviour, attacking family members and other children, shortly after initiating LEV. She had a background history of short febrile convulsions between the ages of 14 months and 3.5 years, but during this period she was otherwise developing and behaving normally.

Her epilepsy developed at the age of 4 years after an episode of viral encephalitis, from which she had initially appeared to have made a full clinical recovery. However, subsequent follow-up showed her behaviour to be disinhibited and excitable.

Four months after the encephalitis episode, she developed intermittent seizures, both tonic clonic and more subtle partial seizures with twitching and vacant episodes. A CT scan and interictal EEG were normal. Carbamazepine was commenced,

but response to increasing doses was incomplete. Moreover, her behaviour became increasingly more difficult with temper tantrums, impulsivity and poor attention. She was referred to a clinical psychologist, and her scores on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI R UK) were found to be low average at 82. However, this may have been underestimated because of poor attention span, and she proceeded to commence mainstream school.

An increase in both tonic clonic and complex partial seizures prompted the introduction of sodium valproate at the age of 5 years 10 months. This led to improvement in tonic clonic seizures but she continued to have "runs" of partial complex seizures, often with an aura of abdominal pain and difficulty in speaking. A trial of lamotrigine at the age of 6.5 years was discontinued after only a few months because of tearfulness, mild agitation and an increase in drop attacks. Gabapentin was introduced at the age of 7 years 2 months, and carbamazepine and sodium valproate were weaned off. Her behaviour at this stage became more challenging with a short attention span, yet she was still manageable at home and at school.

Owing to the persistence of complex partial seizures on gabapentin monotherapy, the decision was made to add levetiracetam at the age of 7 years 5 months. The dose was increased from 250 mg bd (10 mg/kg/day) to 500 mg bd (30 mg/kg/day) over a 3 week period. During the 3 weeks, she was uncharacteristically seizure free. However, her parents described her as being increasingly more difficult, wilful and defiant with increasing temper tantrums. On several occasions she was excluded from school for bad behaviour and repeatedly pinching other pupils. Three weeks after introduction of the LEV therapy, just a few days after reaching the target dose of 500 mg bd, her behaviour became uncontrollable. She was destructive, throwing heavy objects, and assaulting her parents and grandparents. She was admitted into hospital, where she displayed unprovoked and unpredictable mood swings and periods of confusion. She showed violent, aggressive behaviour, and repeatedly attempted to attack nursing staff and fellow patients. She was treated with haloperidol and developed a transient dystonic reaction.

The possibility of an abnormal behavioural response to LEV was entertained and her LEV was discontinued, leaving her on gabapentin monotherapy. Within 5 days of stopping the LEV, her behaviour reverted back to baseline, she was manageable and orientated. Discontinuation of the LEV did, however, lead to the reappearance of both tonic clonic and complex partial seizures.

Risk factors for LEV-induced behaviour dysfunction

The case serves as an example of an adverse drug reaction to a new generation antiepileptic drug which was not highlighted by original clinical trials, and emphasises the need for post-marketing vigilance. Moreover, the case highlights the question as to whether we can identify particular patients at risk of LEV-induced behaviour dysfunction, allowing more careful patient selection when using new antiepileptic drugs.

The analysis of behavioural side effects in LEV clinical trials has already identified previous psychiatric history/behaviour problems, a history of febrile convulsions, and a history of generalised seizures and status epilepticus as being risk factors for behavioural side effects[8,9]. Of interest is that several of these factors apply to our patient.

The rate of dose escalation may also be a factor. In general, tolerability of the new antiepileptic drugs has been found to be greatly improved when dosage is titrated flexibly according to clinical response. For some drugs (tiagabine and topiramate) central nervous system side effects are markedly reduced by starting at a lower dose and increasing very gradually[3].

Moreover, pharmacodynamic interactions involving reciprocal potentiation of neurotoxicity are relatively common when two or more antiepileptic drugs are prescribed simultaneously, which may complicate management[3]. Interestingly, gabapentin has also been associated with behavioural side effects in patients with previous behaviour problems, so the gabapentin-LEV combination probably increased the risk of LEV-induced behavioural side effects in the patient in our case[18].

Epilepsy itself is a risk factor for changes in behaviour with LEV. In the pre-marketing clinical trials programme, LEV was also tested in the elderly with cognitive impairment and in patients with anxiety disorder, all without epilepsy[6,7]. In both of these subgroups the rate of behaviour problems was comparable with placebo controls (6.3% vs 4.1%, and 5.2% vs 5.5% respectively). The epilepsy group, on the other hand, showed 13% behaviour problems versus 6.2% in the placebo group, perhaps suggesting a different response in patients with epilepsy. In other words, some epilepsy patients seem selectively more vulnerable to the toxicity of central nervous system active medications[6]. However, in general, irritability and aggression are not uncommon in epileptic patients, often peri-

ictally. Behaviour changes may also be associated with the underlying aetiology of the epilepsy, such as structural brain lesions, and the effects of the seizures themselves, or subclinical interictal seizure activity[19]. Therefore, care must be taken when differentiating between drug related effects and the impact of medical, psychological and social context of epileptic disease[10].

It is a common experience that the spectrum of side effects of an antiepileptic drug may be different in patients with epilepsy plus significant neurological disability (also called "epilepsy-plus")[20]. In an open study of patients with and without learning difficulties on LEV, there were significantly more side effects in the "epilepsy-plus" group (23% versus 10%)[20]. Several mechanisms may play a role in the increased behavioural side effects profile of patients with learning difficulties/ neurological handicaps:

1. Somatic complaints may be converted into adverse behaviour.

2. Sedative effects of a drug may cause paradoxical reactions (especially in children).

3. Improvement of the condition with reduced epileptiform activity and reduced sedation may lead to an increase in willed behaviour ("release phenomenon" or "forced normalisation")[6].

It may well be that young age is a separate risk factor for LEV induced behavioural side effects, although this remains to be substantiated by controlled clinical trials. Direct application of results from clinical trials in adults is problematic, as paediatric and adult epilepsy are different. There are age related aetiological differences in partial seizures, a higher frequency of localisation related epilepsy syndromes in children, and a higher rate of co-morbidity in children[17]. Moreover, children have a greater chance of "acting out" somatic complaints and of paradoxical reactions to sedative drugs.

Finally, there may well be an association between the underlying pathophysiology of the epilepsy at a molecular level, and the risk of neurobehavioral side effects to certain antiepileptic drugs. Currently, the precise pathophysiological mechanisms responsible for seizure activity in certain individuals are poorly understood. More specific targeting of drugs may well act to dampen, rather than exaggerate, associated behavioural dysfunction.

Conclusion

Levetiracetam has, in the post-marketing phase, been associated with behavioural side effects in both adults and children. There seem to be certain risk factors for behavioural side effects such as pre-existing behaviour disturbance or psychiatric disorder, learning difficulties, young age and rapid titration of drug therapy. Patients with risk factors should be counselled, paralleled by close follow-up and early intervention if needed[10]. Slow titration starting at 10 mg/kg and increasing over 4 weeks to 20 mg/kg is recommended, followed by continued slow titration to a maximum of 40 mg/kg/day[5]. We anticipate further advances in pharmacogenetics and the molecular pathophysiology of epilepsy, leading to individually tailored, effective drug treatment with a reduced side effect profile[21].

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