Safety profile of levetiracetam

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ABSTRACT − A good balance between safety and tolerability is necessary for an antiepileptic drug (AED) to be successful in the management of patients with epilepsy. Levetiracetam is one of the new generation of AEDs licensed as an add-on therapy for the treatment of patients with partial-onset seizures. Levetiracetam’s mechanisms of action are not fully understood. Controlled clinical trials, open-label studies, and postmarketing surveillance indicate that levetiracetam has a favorable safety profile characterized by little effect on vital signs or clinical laboratory values, reported adverse events that are mild to moderate, and no known drug-drug interactions. The tolerability of levetiracetam may extend to both pediatric and elderly patients based on analyses of small numbers of patients. Tolerability is maintained over the long term. Levetiracetam does not appear to have a different safety profile in learning-disabled patients. Levetiracetam appears to have a good balance between tolerability and efficacy in the treatment of a wide variety of patients with partial epilepsy.

KEY WORDS: epilepsy, antiepileptic drugs, seizures, levetiracetam, drug-drug interactions, safety profile

Introduction

Until about 10 years ago, physicians had limited choices for the control of seizures in patients with epilepsy [1]. However, an ‘explosion’ in the development of antiepileptic drugs (AEDs) began in the 1990s and continues today [2]. While these new treatment options offer significant potential benefit to patients with seizure disorders, the risks associated with their use must also be evaluated [3]. Side-effect profiles may differ considerably from one agent to another and represent a major factor in determining choice of treatment. At present, information about the comparative safety of new AEDs is somewhat limited [4]. Continual monitoring is required to establish long-term safety in large numbers of patients with varied demographic and clinical characteristics.

Compared with both classic and newer AEDs, levetiracetam’s (Keppra) low incidence of adverse effects results in an unusually high safety margin in animal models reflecting both partial and primary generalized epilepsy [5]. Levetiracetam shows an absence of negative impact on cognitive function in normal and kindled rats, unlike classic AEDs [6].

The objectives of the present review are to summarize information regarding the short- and long-term safety of levetiracetam in controlled clinical trials, present data on the long-term safety of levetiracetam from open-label studies, review the data to support a claim for lack of drug-drug interactions, and summarize limited safety data for levetiracetam in special patient populations (pediatric patients, the elderly, women of childbearing age, and the learning-disabled).

¹. Keppra is a registered trademark of UCB S.A.
Safety data from controlled clinical trials

Randomized controlled clinical trials in which levetiracetam was administered in combination with other AEDs or as withdrawal to monotherapy for refractory partial seizures have shown that it is well tolerated [7-13]. The three pivotal trials of levetiracetam were multicenter, double-blind, placebo-controlled studies that included 904 adults with refractory partial seizures with or without secondary generalization who were randomized to treatment with placebo or 1000, 2000, or 3000 mg/day of levetiracetam in conjunction with other AEDs (e.g., carbamazepine, phenytoin, phenobarbital, primidone, clonazepam, valproate, vigabatrin, lamotrigine, and gabapentin) [7-9]. In one of these trials, responders were converted to monotherapy [7]. A fourth study included 119 patients randomized to treatment with placebo or 2000 or 4000 mg/day of levetiracetam as add-on therapy [10].

Vital signs and clinical laboratory values

Levetiracetam had no significant effects on blood pressure, pulse rate, or electrocardiograms (ECGs) [7-10]. A separate analysis of the effects of levetiracetam on body weight indicated that it had no effect on body weight in either male or female patients [14]. Levetiracetam had minimal or no effects on clinical laboratory values. Levetiracetam has been associated with slight reductions in red blood cell counts, hematocrit, and hemoglobin; however, all values remained within the normal range [13]. Mean white blood cell (WBC) counts also remained within the standard laboratory normal range during and after treatment with levetiracetam. Moreover, drug discontinuation was not necessary in any patient because of neutropenia [13].

There were no significant changes in blood chemistry associated with levetiracetam therapy. Most importantly, there were no statistically significant elevations in liver function tests (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, total bilirubin, or alkaline phosphatase) among patients who received levetiracetam in placebo-controlled trials [13].

Adverse events

Adverse events reported most often are summarized in table 1 [11]. In controlled clinical trials, 15.0% of patients treated with levetiracetam discontinued therapy or had their dose reduced due to adverse events, versus 11.6% of those who received placebo [11, 12]. The adverse events most commonly associated with discontinuation or dose reduction in patients treated with levetiracetam were somnolence (4.4% versus 1.6% for placebo), convulsions (3.0% versus 3.4%), dizziness (1.4% versus 0%), asthenia (1.3% versus 0.7%), and rash (0% versus 1.1%). The majority of adverse events were mild to moderate in severity. Overall, 14.7% (113/769) of the patients taking levetiracetam and 11.2% (49/439) of those who received placebo experienced severe adverse events. Those events occurring at greater than 0.5% and with an incidence more common in the levetiracetam group were somnolence, 3.1% (0.9% for placebo group); asthenia, 1.6% (0.5% for placebo group); convulsion, 1.6% (1.4% for placebo group); grand mal convulsions, 1.0% (0.9% for placebo group); dizziness, 0.7% (0 for placebo group); depression, 0.7% (0 for placebo group); and personality disorder, 0.5% (0 for placebo group) [12].

Seizure exacerbation

Unexpected exacerbation of seizures can occur during treatment with AEDs [15-18]. Worsening of seizures may occur in patients treated with levetiracetam. Data from placebo-controlled trials have shown that worsening of seizures (increase of > 25%) was seen in 14% of levetiracetam patients, compared to 26% of placebo patients ($P < 0.001$) [13, 19]. No definite relationship with dose was observed.

Table 1. Incidence of adverse events occurring in at least 1% of levetiracetam-treated patients and occurred more frequently than placebo-treated patients in placebo-controlled clinical trials [11]

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Levetiracetam (N = 769)</th>
<th>Placebo (N = 439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Infection</td>
<td>13%</td>
<td>8%</td>
</tr>
<tr>
<td>Pain</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Digestive system</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Nervous system</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Amnesia</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Depression</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Hostility</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Cough increased</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Special senses</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Safety from long-term extension studies

While results from short-term clinical trials are essential for establishing the safety of an AED, they are not powered to provide information about the occurrence of rare adverse events [20] and are not of sufficient duration to permit the identification of side effects that occur only with long-term drug exposure. Thus, data from long-term, often open-label, evaluations provide an essential component of the safety profile for any drug product.

Krakow et al. [21] assessed the long-term open-label efficacy and safety of levetiracetam in 1422 patients who were followed for up to 5 years. During this period, 15.8% (225) of patients discontinued levetiracetam due to adverse events, most often convulsions (3.4%), somnolence (2.0%), asthenia (0.6%), depression (0.6%), dizziness (0.5%), and headache (0.5%). These events are similar to those reported in the shorter-term placebo-controlled studies and support the view that long-term use of this AED does not appear to be associated with the development of unexpected adverse events.

Postmarketing surveillance

The spontaneous reporting of adverse events to surveillance programs such as MEDWATCH is important for determining the safety profile of any drug, and is particularly useful for revealing unusual or rare adverse events [22-24]. Such surveillance has provided safety data for levetiracetam consistent with that summarized in the preceding sections.

Other tools for measuring reported side effects in clinical use have revealed a similar profile as well. Sadek and colleagues, of the University of Pennsylvania School of Medicine in Philadelphia, analyzed data on behavioral side effects in patients starting treatment in the Postmarketing Antiepileptic Drug Survey (PADS) database [25]. The database is a prospective registry that pools information from 16 epilepsy centers to study patients treated with new AEDs.

Several small-scale studies report behavioral adverse events [26-36]. The behavioral adverse event rate from the PADS registry (N = 288) is nearly identical to that obtained in the premarketing data. Of 288 patients initiating levetiracetam therapy who had a mean follow-up of 240 days, 75 (23.8%) reported behavioral problems. Behavioral adverse events led to the discontinuation of levetiracetam in 27 patients (8.5%).

Behavioral adverse events in the PADS registry included irritability in four patients, aggression in five (all of whom were mentally retarded), depression in 14, anxiety in eight, and mood swings in three; the type of behavioral problem was unspecified in five patients (table 2). A history of past psychiatric/behavioral problems/mental retardation was noted in 51.2% of patients with behavioral adverse events, versus 49.6% of the total levetiracetam group [25].

Psychiatric symptoms are common in many patients with epilepsy [37]. Indeed, behavioral disturbances and psychotic reactions appear to be more prevalent in patients with refractory epilepsy than in the population at large, and sometimes have been associated with AED therapy [38]. Therefore, the findings of behavioral adverse events in randomized, double-blind trials with levetiracetam are not unexpected. Such reactions can be seen, for example, when patients with previously intractable epilepsy suddenly become seizure-free [39]. Older drugs most often associated with psychobehavioral disturbances in patients with epilepsy include phenobarbital and phenytoin [40]. Among the newer agents, vigabatrin, zonisamide, topiramate, and gabapentin appear to have raised concern regarding psychiatric adverse events [38, 40-44].

In addition to the adverse experiences summarized in table 1, the following have been reported in patients receiving levetiracetam postmarketing: leukopenia, neutropenia, pancytopenia, and thrombocytopenia. However, the data are insufficient to support an estimate of their incidence or to establish causation.

While postmarketing surveillance safety data must be viewed with some caution, particularly with respect to the assignment of causality for reported events [23, 45], the results available to date for levetiracetam are consistent with the view that long-term use of this AED in the normal clinical setting is not associated with the emergence of new and life-threatening adverse events not observed in shorter-term controlled clinical trials. However, the total patient exposure to date (197 634 patient-years as of December 2002) is still not enough to rule out the possibility of very rare severe idiosyncratic adverse events [24].

Drug-drug interactions

Drug-drug interactions affecting AED metabolism occur often but may be unpredictable [46]. Treatment with some AEDs is complicated by the fact that they may induce or inhibit the activity of key hepatic enzymes that catalyze oxidative reactions important for drug clearance. Treat-

Table 2. Behavioral adverse events reported in postmarketing use database for levetiracetam [25]

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number (%) of patients (N = 288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>14 (4.9%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8 (2.8%)</td>
</tr>
<tr>
<td>Aggression</td>
<td>5 (1.7%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Mood swings</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>5 (1.7%)</td>
</tr>
</tbody>
</table>
ment with such drugs can influence both their own metabolism and that of other medications.

Some of the newer AEDs have a substantially lower potential for drug-drug interactions than the older AEDs, including phenytoin, valproate, and carbamazepine. The pharmacokinetic profile of levetiracetam suggests that it has a very low potential for clinically significant drug-drug interactions, and this has proven to be the case. Levetiracetam is not protein bound (<10% bound), and its volume of distribution is close to the volume of intracellular and extracellular water [47]. Sixty-six percent of a levetiracetam dose is excreted unchanged in urine. The major metabolic pathway (24% of dose) involves enzymatic hydrolysis of the acetamide group, which is not hepatic CYP-dependent. The metabolites of levetiracetam have no known pharmacologic activity and are also excreted via the kidney [47].

Levetiracetam does not interfere with the metabolism of other AEDs, and other drugs used to control seizures do not significantly affect the pharmacokinetic profile of levetiracetam [11, 47]. Studies with agents well known to cause drug interactions (e.g., phenytoin, oral contraceptives, digoxin, and warfarin) showed no evidence of any pharmacokinetic interaction with levetiracetam [48-51]. Administration of probenecid, an inhibitor of renal tubular secretion, did not change the pharmacokinetics of levetiracetam but did reduce the clearance of the primary metabolite (ucb L057) by 60%. This effect was probably a result of competitive inhibition of tubular secretion of ucb L057 by probenecid [11].

Safety in special patient populations

Both children and elderly patients are especially prone to have epilepsy. In both populations, the selection of AEDs has to take into account the different pharmacokinetics and sensitivity to adverse events [52-58]. Women are considered a special patient population because of issues related to contraception, childbirth, and breast-feeding. Finally, the learning-disabled or cognitively impaired also constitute a special patient population. These patients may be particularly vulnerable to the neurotoxic and sedative effects of some AEDs, and inappropriate treatment may exacerbate their intellectual impairment [59].

Pediatric patients

Results from a small-scale study (N = 24) suggest that levetiracetam may be safe and well tolerated in pediatric patients with epilepsy [60]. The types and rates of side effects in children in this study appear generally similar to those reported in adults.

Glauser et al. administered levetiracetam to 24 children between 6 and 12 years of age with treatment-resistant partial-onset seizures [60]. The most commonly reported adverse events were headache (33%), infection (33%), anorexia (25%), and somnolence (25%). Two patients experienced changes in laboratory values (a decrease in red blood cell count and an elevation in mean corpuscular volume) that were considered clinically significant. There were no significant effects on physical or ECG findings. Five patients experienced ≥7% changes in body weight (three increased and two decreased). The safety profile for levetiracetam appeared similar to that in adult patients. The similarity of the adverse event profiles for levetiracetam in adult and pediatric patients is further supported by recent results from Hovinga et al. [61], who retrospectively evaluated 77 adults and 27 children (median age 12 years) treated with this AED. Adverse events occurred in 56% of the adults and 52% of the children over an average of approximately 5 months of follow-up. Adverse events resulted in discontinuation of levetiracetam in 14% of the adults and 11% of the children. The most common adverse events in the two groups were somnolence, dizziness, depression, increased seizure frequency, and cognitive changes, and they occurred with approximately equal frequency in the two groups.

The elderly

Kraemer and Edrich [32] evaluated safety data for levetiracetam in all patients ≥50 years of age who were treated with this AED during clinical development for epilepsy. Their retrospective analysis included 211 patients with a median age of 56 years (range, 50 to 78 years), including 14.7% older than 65. The mean duration of exposure was 697 days (range, 1 to 2409 days), the median dose, 3000 mg/day. At the end of the observation period, 43.6% of patients were still receiving levetiracetam; 19.9% of the patients had discontinued treatment due to adverse events. When these researchers compared the adverse events of the older individuals to those of the total population of patients (1422) who received levetiracetam during the same period, the types and rates of adverse events were generally the same. The adverse events reported most often involved the central nervous system (e.g., somnolence, asthenia, dizziness) and were generally mild in severity. Thus, the safety profile for levetiracetam in older patients is very similar to that in younger adults. No dosing modifications for levetiracetam are required in the elderly except as indicated by their renal function [52].

Women of childbearing age

In women with epilepsy, drug-related issues include the alteration of menstrual cycles, interactions with oral contraceptives, and potential risks to the fetus. As already noted, levetiracetam does not influence the efficacy of oral contraceptives [51, 62]. Due to its recent marketing, its potential for teratogenesis is still unknown. However, preclinical data in animals suggest the potential is low [63]. As with other AEDs, levetiracetam can be used during pregnancy if the potential benefits justify the possible
risks. Additional prospective data must be collected to determine the effect of levetiracetam on pregnancy and its outcome. Like many other drugs, levetiracetam is excreted in breast milk. The American Academy of Neurology has issued some recommendations on the issue of breastfeeding while on AEDs [64]. It has been advocated that a risk-benefit analysis should be done with the mother in order to make a decision. In general, breastfeeding is encouraged, unless untoward side effects are observed in the child.

The learning disabled

The safety of levetiracetam in patients with learning disabilities has not been evaluated. Kaplan [65] carried out a retrospective chart review of 28 developmentally delayed and/or mentally retarded patients with epilepsy who were treated with levetiracetam. Only one adverse event (somnolence) was noted. O’Rourke et al. [66] administered levetiracetam as add-on therapy to 18 learning-disabled adults with intractable seizures. Over 3 months of follow-up, one patient discontinued due to an adverse event (postictal psychosis). While very limited, these results suggest that levetiracetam therapy may be safe for this patient group.

Patients with renal impairment

No dosing adjustment is required for levetiracetam in patients with solely hepatic impairment, but dosing must be adjusted in patients with renal impairment based on creatinine clearance.

Conclusions

Levetiracetam is a safe AED for the adjunctive treatment of partial epilepsy. Adverse events are relatively infrequent and usually mild. The most frequent CNS-related adverse events include asthenia, fatigue, dizziness, and somnolence. Levetiracetam has little effect on vital signs or clinical laboratory values. Although there have been some reports of behavioral disturbances in patients taking levetiracetam, the frequency of reported symptoms appears to be low. The tolerability of levetiracetam is maintained over the long term and could extend to pediatric and elderly patients as well as those with learning disabilities.

References


