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Long-term experience with levetiracetam

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ABSTRACT – Although short-term clinical trials provide important data regarding efficacy and tolerability, long-term studies are needed to address important aspects of clinical practice, such as long-term efficacy and safety. Long-term studies and post-marketing data show that the efficacy of levetiracetam is sustained over the long term and that this antiepileptic drug continues to be well tolerated, with low withdrawal rates and high retention rates. Patients continue to achieve significant reductions in seizure frequency and may achieve seizure freedom. Levetiracetam may allow patients to decrease the number of concomitant antiepileptic medications or withdraw to monotherapy. Add-on therapy with levetiracetam should be considered when additional control of seizures is needed.

KEY WORDS: epilepsy, AEDs levetiracetam, long-term therapy, seizures

Introduction

The efficacy and tolerability of new antiepileptic drugs (AEDs) are usually evaluated in clinical trials of short duration, typically 3 months. In the pivotal trials of levetiracetam, the selection visit was generally followed by an 8- to 12-week baseline period, 4-week titration period, 14- to 18-week evaluation period, and 8- to 12-week withdrawal period (or option to enter a follow-up study) [1-3]. These well-controlled short-term clinical trials showed levetiracetam to be both effective and well tolerated, whether the drug was given as add-on therapy or patients were withdrawn to monotherapy. Many refractory patients achieved reductions of 50% or greater in seizure frequency, and some achieved seizure freedom. Adverse events tended to be mild to moderate in severity.

The efficacy and tolerability of levetiracetam are enhanced by its unique pharmacokinetic profile. It is quickly and almost entirely absorbed following oral administration and exhibits linear kinetics and minimal protein binding [4]. In addition, levetiracetam undergoes minimal non-hepatic metabolism; approximately 66% of the dose is excreted unchanged in urine. This profile suggests a low risk of drug interactions [4].

Although the data provided by these clinical trials are immeasurably valuable, long-term studies are needed to address other aspects of therapy important to practicing physicians. Long-term efficacy and safety can only be assessed by long-term studies. Post-marketing experience can also provide extremely useful information about freedom from seizures and drug tolerance, assessed in a more general patient population.

This article summarizes the long-term data available to date for levetiracetam and presents postmarketing data on efficacy, including freedom from seizures, loss of efficacy, retention rates, and reasons for withdrawal.

Long-term data

Data for all 1422 patients exposed to levetiracetam during the development

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program in the US and Europe have been analyzed [5, 6]. All patients had refractory epilepsy and received levetiracetam as add-on therapy. A number of parameters were evaluated, including change in seizure frequency, seizure freedom, adverse events, reasons for withdrawal, and retention rate.

Of the 1422 patients included in this study, 95% of patients had localization-related epilepsy at baseline; 78.2% had complex partial, 27.6% simple partial, and 24% secondarily generalized seizures [5]. The majority of these patients were being treated with levetiracetam and one (42%) or two (45%) other AEDs, most commonly carbamazepine (61%), valproate (24%), and/or phenytoin (23%).

Given that the long-term database was compiled from a number of clinical studies, dosage varied. The median starting dose was 1000 mg/day; the median daily dose was 3000 mg/day for adults, 2000 mg for the elderly, and 1250 mg for children [5].

Overall, 38.6% of patients exhibited a 50% or greater reduction from baseline in total seizure frequency, and 20% of patients exhibited at least a 75% reduction compared to baseline [5]. By the end of the treatment period, 14.4% of patients were able to decrease the number of concomitant AEDs, and 5.5% of patients achieved levetiracetam monotherapy [6].

Although efficacy is usually defined as at least a 50% reduction in seizure frequency, seizure freedom is the ultimate goal of AED therapy. Evaluation of the data for these 1422 patients demonstrated that 65 (4.6%) patients were seizure-free from day 1 of treatment. One hundred eighty-three (12.9%) achieved seizure freedom for at least six consecutive months, and 109 (7.7%) were seizure-free for at least 12 consecutive months [5]. Of the 491 patients who were being treated with one AED when levetiracetam was added, 97 (19.8%) achieved seizure freedom during the last 6 months of treatment [6].

The most common drug-related adverse events included headache, somnolence, asthenia, and dizziness [5]. Events suggestive of changed behavior were rare [6]. There were no reports of idiosyncratic side effects or serious hematologic or biochemical abnormalities. A total of 225 (15.8%) patients withdrew due to adverse events, most commonly convulsions and somnolence, while 261 (18.4%) withdrew due to lack or loss of efficacy [5].

Based on Kaplan-Meier survival analysis, the estimated continuation rate of levetiracetam treatment was 60% after 1 year, 37% after 3 years, and 32% after 5 years [5]. Cox regression analysis identified the following factors as having a positive effect on retention rate: high maximal doses, low starting doses, the presence of generalized seizures, and fewer concomitant AEDs at baseline [5].

The majority of withdrawals from levetiracetam treatment occurred within the first year, after which retention rates remained almost constant [5]. This suggests that patients who respond over the short term are unlikely to experience resistance, or tolerance, to levetiracetam after prolonged exposure.

Seizure freedom over time can also be used as an indirect measure to predict the likelihood of drug tolerance. Additional analyses showed that 11.7% (167/1422) and 8.9% (126/1422) of the patients exhibited seizure freedom during the last 6 and 12 months of treatment, respectively [6]. Additionally, nearly one half of evaluable patients (41.5%; 548/1321) exhibited at least a 50% reduction in seizure frequency, and 26.9% (355/1321) exhibited at least a 75% reduction in the last 6 months [6]. Responder rates were similar during the last year of treatment, with 40.5% (536/1325) and 24.9% (330/1325) of patients exhibiting at least 50% and 75% reductions in seizure frequency, respectively [6].

To further evaluate how well efficacy was maintained, investigators examined how many patients who initially exhibited 50% and 75% reductions in seizure frequency remained in that category at two subsequent 3-month visits. Of the 39.2% (519/1325) of patients who exhibited a 50% reduction in seizure frequency at visit 1, 73.6% (382/519) remained responsive at visit 2, and 82% (314/382) of these were still responders at visit 3. Of the 20% (265/1325) of patients who exhibited a 75% reduction in seizure frequency at visit 1, 71% (189/265) remained responders at visit 2, and 82% (155/189) were still responders at visit 3.

Among patients receiving levetiracetam and only one concomitant AED (n = 491), response rates observed for the overall treatment period were similar to those seen during the last 6 months of treatment. Overall, 40.4% (182/451) and 22% (99/451) of patients experienced reductions in seizure frequency of at least 50% or 75%, respectively, compared to 43.1% (194/450) and 29.1% (131/450), respectively, during the last 6 months of treatment. Approximately 20% (97/491) of patients were seizure-free during the last 6 months of levetiracetam treatment.

Postmarketing data

The medical records of all patients started on levetiracetam therapy by the authors between April 2000 and August 2001 were analyzed. Patients previously enrolled in completed levetiracetam trials or already taking levetiracetam at the time of presentation were excluded. Seizure and epilepsy characteristics; baseline AEDs; levetiracetam dose, including starting dose, initial target dose, maximal dose, and final maintenance dose; seizure counts at baseline and at follow-up; and behavioral adverse events (AEs) were recorded. The response to levetiracetam in the first 3 months of treatment was categorized as: seizure-free, ≥ 90% seizure reduction, ≥ 50% seizure reduction, or < 50% seizure reduction. Also identified were patients achieving ≥ 50%, ≥ 90%, and 100% seizure reduction for

the last 3, 6, and 12 months at last follow-up. Excluded from this count were patients who became seizure-free after epilepsy surgery during treatment with levetiracetam. Patients not seen within 6 months of the analysis were called for an update, and this information was entered into a computerized database. The protocol was approved by the Vanderbilt University Institutional Review Board.

The total group included 215 patients (119 female). All but 13 were older than 18, and only two were younger than 10 years of age. The epilepsy classification was localization-related in 168 and generalized in 47. At the last follow-up (clinic visit or telephone contact), 155 (72.1%) patients were continuing treatment; 93 had been treated for at least 2 years. Twenty-five (11.6%) patients had been seizure-free for at least 1 year, 33 (15.3%) had been seizure-free for at least 6 months, and 44 (20.5%) had been seizure-free for at least 3 months. Over the last year, 41 patients (19.1%) had experienced a reduction in seizures of at least 90%, and 103 (47.9%) a reduction of 50% or greater (*table 1*). There was no significant difference in response between patients with localization-related epilepsy and those with generalized epilepsy. However, one specific generalized epilepsy syndrome was associated with a particularly favorable response. Juvenile myoclonic epilepsy (JME) had been diagnosed in 16 patients, 14 (87.5%) of whom were continuing levetiracetam at the last follow-up. Five (35.7%) of these 14 patients had been seizure-free for at least 1 year, and three others were nearly seizure-free, with only rare myoclonic jerks related to sleep deprivation or missing their levetiracetam doses. Four of these eight patients were on levetiracetam monotherapy, with a mean dose of 1312 mg/day. Many patients who were counted as non-responders (< 50% reduction) had a reduction in seizure severity, including a switch from complex partial to simple partial seizures, or from secondarily generalized to complex partial seizures.

The final mean levetiracetam dose for seizure-free patients was significantly lower than that for non-responders (1704 versus 2333 mg/day, $P = 0.0001$, two-tailed non-paired *t*-test). There was also a non-significant trend for a lower mean dose in ≥ 90% responders who were not seizure-free (final mean daily dose 1868 mg, $P = 0.088$, two-tailed non-paired *t*-test). However, the mean dose was identical for responders with < 90%, but ≥ 50% seizure reduction and non-responders.

Table 1. Responder rates in post-marketing analysis*

	For ≥ 3 months	For ≥ 6 months	For ≥ 1 year
Seizure-free	44 (20.5%)	33 (15.3%)	25 (11.6%)
≥ 90% seizure reduction	63 (29.3%)	53 (24.7%)	41 (19.1%)
≥ 50% seizure reduction	122 (56.7%)	114 (53.0%)	103 (47.9%)

*Percentages are based on total number of patients started on levetiracetam ($n = 215$).

Levetiracetam was combined with one other AED in 119 patients, with two AEDs in 76 patients, and with three AEDs in six patients. Fourteen were on montherapy. The relationship between seizure response and concomitant AED therapy was analyzed to investigate the effectiveness of specific AED combinations. The authors had made the anecdotal observation that levetiracetam was particularly effective in combination with lamotrigine. Lamotrigine was the only adjunctive AED in 57 patients and one of two or more adjunctive AEDs in 50 others. The corresponding numbers for single or multiple adjunctive therapy for other AEDs were 24 and 15, respectively, for carbamazepine, 5 and 11 for phenytoin, 11 and 5 for oxcarbazepine, 2 and 13 for topiramate, 3 and 8 for zonisamide, 0 and 11 for clonazepam, and 8 and 9 for valproate. When ≥ 90% and ≥ 50% seizure reduction were calculated in patients taking levetiracetam with only one other agent, there was no significant difference between the levetiracetam and lamotrigine combination and levetiracetam plus an AED other than lamotrigine. At 1 year, seizure reduction ≥ 90% was seen in 20.8% and 23% of patients, respectively, while seizure reduction ≥ 50% was seen in 54.7% and 60.7% of patients. This finding could potentially be an artifact of the attempt to convert refractory patients to the levetiracetam plus lamotrigine combination, while keeping those who are responsive on their original AED.

The development of tolerance was assessed by comparing response to therapy in the first 3 months versus the last 3 months of therapy. Only five patients (18.5%) of those seizure-free in the first 3 months of treatment were no longer seizure-free at last follow-up, but all five were still ≥ 50% improved and four were ≥ 90% improved at last follow-up. On the other hand, 17 patients (39% of those who were seizure-free at last follow-up) were not seizure-free initially and became seizure-free at the last follow-up.

Among patients who stopped treatment, only 21 (10%) discontinued because of AEs (psychiatric/behavioral in 10, other in 11). Twenty (9%) cited lack of efficacy, 10 (5%) lack of efficacy and AEs (psychiatric/behavioral in six, other in four). Three (1.4%) died; one died of another disease, one died accidentally, and one committed suicide in the setting of intractable pain and adverse social factors. Six (3%) discontinued for other reasons. Thus, the most likely AEs to contribute to the discontinuation of levetiracetam were behavioral (16 patients [7%]). These were always reversed following drug withdrawal or dose reduction. The most common behavioral AEs were irritability, agitation, inner feeling of aggression, or moodiness. When lumped together, these were reported in 23 (10.7%) patients, but they varied in severity. Depression was reported in three patients (1.4%) but resolved: one patient had no significant seizure reduction and stopped levetiracetam,

while the other two, who were responders, continued the drug at lower doses. Psychotic delusions occurred in three patients (1.4%) and nonpsychotic visual hallucinations in one (0.5%). All four stopped levetiracetam and fully recovered. There was a non-significant trend for a lower levetiracetam dose in patients experiencing behavioral AEs (1858 versus 2155, $P = 0.16$, 2-tailed *t*-test), suggesting that these AEs inhibited further dose increases. Shortly after marketing, most patients were started on 500 mg bid orally without titration. Based on the preliminary observation that some behavioral AEs improved with dose reduction, after about 1 year, most patients were started on 250 mg once or twice daily. When we compared the incidence of behavioral AEs in those started on 500 mg bid without titration and those started on a smaller dose, there was no difference. A slower titration was not associated with fewer behavioral AEs. Thus, behavioral AEs were predominantly idiosyncratic.

Quality of life

Patients' expectations and perceptions of efficacy clearly play a role in their decision to continue therapy. Quality of life therefore becomes an important issue. One of the secondary end points of a short-term levetiracetam trial done in the US assessed quality of life in 246 patients using a quality-of-life questionnaire. These patients reported significant improvements in the areas of seizure worry, overall quality of life, and cognitive functioning [7]. In a long-term extension, in which 101 of these patients were followed for approximately 4 years, these improvements were sustained [8].

Conclusions

Short-term clinical trials have demonstrated that levetiracetam is highly effective and well tolerated in patients with refractory partial-onset seizures. In a US trial, 33% of patients taking 1000 mg/day and 40% of patients taking 3000 mg/day exhibited a 50% or greater reduction in partial seizure frequency over the evaluation period compared to baseline, and 5.5% of the patients became seizure-free [1]. In a similar European trial, 23% of patients taking 1000 mg/day and 32% taking 2 000 mg/day exhibited a 50% or greater reduction in seizure frequency compared to baseline [2]. Levetiracetam also proved effective and well tolerated when given as monotherapy to patients with refractory partial seizures who had responded well to add-on therapy: 59% of patients exhibited a 50% or greater reduction in seizure frequency, and a median reduction of 74% in seizure frequency was attained, with 18% of patients remaining seizure-free [3]. In each of these studies, adverse events were generally mild to moderate in severity.

Long-term and post-marketing data suggest that tolerance is not likely with levetiracetam therapy. It is much more likely that seizure freedom develops with titration of levetiracetam after an initial partial response. The post-marketing data indicate that seizure-free patients require a significantly lower dose than non-responders, suggesting that an excellent response can be predicted early. This represents a distinct advantage in comparison with agents requiring long periods of titration.

Although no head-to-head comparative studies have been done, a review of the literature suggests that levetiracetam compares favorably with topiramate, gabapentin, lamotrigine, and vigabatrin in terms of both long-term efficacy and tolerability [9-12]. Wong *et al.* reported a modest long-term effect for gabapentin, lamotrigine, and vigabatrin in patients with intractable epilepsy [9]. Sander *et al* reported marked improvement in seizure frequency in a group of patients taking lamotrigine, but no patients achieved seizure freedom [10]. In a meta-analysis of levetiracetam, oxcarbazepine, remacemide, and zonisamide, levetiracetam had the more favorable "responder-withdrawal ratio," followed by zonisamide and oxcarbazepine [13].

As previously stated, the ultimate goal of AED therapy is seizure freedom. Although most patients respond to treatment with AEDs, more than 30% remain refractory [14]. Levetiracetam has been shown to be highly effective and well tolerated in patients with refractory epilepsy in both short- and long-term studies, and post-marketing data support these findings.

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