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Preliminary efficacy of levetiracetam in monotherapy

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ABSTRACT – The standard of care for prescribing antiepileptic drugs (AEDs) has come to favor the use of monotherapy when possible; i.e., when comparable efficacy can be achieved with fewer risks of adverse events and drug interactions. Most patients with epilepsy are started on one of the classic AEDs and, if it proves ineffective, another drug is tried, usually as monotherapy. While most of the newer AEDs that have come into clinical use in recent years are initially used as add-on therapy, their success at improving seizure control in combination treatments has led to their cautious use as monotherapy even before they have been approved for this indication. As a first study to determine the potential efficacy of levetiracetam in monotherapy, a withdrawal trial model was used. Patients who achieved adequate seizure control with levetiracetam as add-on therapy in a double-blind, placebo-controlled study entered a monotherapy phase of the trial in which the baseline AED was gradually withdrawn. Also, long-term data of 505 patients who received levetiracetam for refractory partial seizures were reviewed and found to include 49 patients still treated with levetiracetam monotherapy at the end of the study for a duration between 3 months and 5.5 years. Data from patients in the two trials lend supportive evidence that levetiracetam monotherapy is safe and effective for partial seizures.

KEY WORDS: levetiracetam, antiepileptic drugs, monotherapy, epilepsy

Introduction

The management of epilepsy has become more sophisticated in recent years as our understanding of epileptic syndromes and their classification has improved and the number of effective agents has increased. The optimal management of the epileptic patient involves making a precise diagnosis—based on precipitating factors, seizure type, age at onset, family history, and interictal EEG abnormalities—and using that information to choose a rational treatment plan [1].

Historically, patients with epilepsy were treated with multiple agents from the outset. This approach was based on the belief that two agents worked synergistically, resulting in better seizure control with fewer side effects, since lower doses of each drug were necessary [2]. This approach, which lacked a scientific rationale and was not based upon empirical evidence, has been superceded in recent decades by a strong preference for monotherapy. It appears in a large number of patients that monotherapy is as effective as polytherapy but with fewer side effects and drug interactions. When two drugs with similar dose-related side-effect profiles are taken at therapeutic doses, drug-drug interactions may magnify the risk for side effects [3]. Studies have shown that in up to 70% of patients with new-onset seizures, monotherapy

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with any one of the standard or new antiepileptic drugs (AEDs) will result in adequate seizure control [1]. For those who do not achieve adequate control on a single drug, rationally chosen polypharmacy may be necessary and beneficial [3].

The six classic AEDs—phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide, and valproate—are still often used as the drugs of first choice for the initiation of epilepsy therapy. However, up to 30% of patients may not respond adequately regardless of drug choice [1]. Newer drugs approved for clinical use in recent years can complement the older AEDs when used in combination [1, 2]. The newer drugs have proven to be effective as add-on therapy. Their adverse event profiles, particularly with regard to somnolence, have frequently been more favorable than those of the classic AEDs, suggesting that some patients may do better on monotherapy with a newer agent than with a classic agent [1]. In fact, their tolerability and ease of use suggest that many of the newer AEDs are attractive candidates for monotherapy even at the start of therapy.

The new-generation AEDs may be effective as monotherapy even in patients who have been refractory to therapy with classic agents [4-7]. Data are accumulating from a variety of clinical trials suggesting that levetiracetam, currently approved for clinical use as an adjuvant AED for the treatment of partial-onset seizures with and without secondary generalization, may soon join those new AEDs effective in monotherapy.

Mechanism of action of levetiracetam

The mechanism of action of levetiracetam is not related to that of any of the AEDs currently in use [8]. The precise mechanism of antiepileptic action for levetiracetam is still unclear. Unlike most other AEDs, levetiracetam is without significant activity in several animal models involving acute single seizures induced in normal animals by maximal stimulation with electrical current or different chemoconvulsants but has demonstrated seizure protection in animals with genetic or kindled epilepsy, and in models in which chemical convulsants were used to produce seizures mimicking partial epileptic seizures in man [9]. Moreover, in these animal studies, levetiracetam demonstrated an unusually high safety margin.

Other studies have shown that levetiracetam lacks any effect on neuronal Na^+ channels, low voltage-activated T-type Ca^{2+} channels, or ionotropic excitatory glutamate receptors and any direct effect on GABA or glycine-dependent inhibitory currents [10-12]. These targets account for most of the known mechanisms of action of both the classic and newer anticonvulsants. (For a more complete discussion of the mechanism of action of levetiracetam, see the article by Drs. Klitgaard and Pitkänen in this supplement.)

Levetiracetam as add-on therapy

Levetiracetam administered as adjunctive therapy to patients with refractory partial-onset seizures who have failed at least two other AEDs has been evaluated in three placebo-controlled, pivotal trials with double-blind evaluation periods ranging from 12 to 14 weeks [13-15]. In one multicenter study conducted in the United States, 294 patients were randomized to receive placebo, levetiracetam 1000 mg/day, or levetiracetam 3000 mg/day [13]. Patients receiving both levetiracetam doses had a significantly better reduction in partial seizure frequency compared with placebo and a significantly better responder rate. Seizure reduction was observed for all seizure sub-types. The other two studies were conducted in Europe. In one, 324 patients were randomized to receive placebo, levetiracetam 1000 mg/day, or levetiracetam 2000 mg/day [14]. Here too, the groups treated with levetiracetam responded significantly better than those receiving placebo in seizure frequency and responder rate. In the second European study, 286 patients were randomized to receive placebo or 3000 mg/day of levetiracetam [15]. The patients receiving levetiracetam had significantly fewer seizures than patients receiving placebo. In all three studies, statistically significant seizure freedom rates were observed with levetiracetam at the 3000 mg dose level. Moreover, levetiracetam was well tolerated in all three studies. The most common adverse events considered drug-related by the investigators were somnolence, asthenia, headache, and dizziness.

A pooled analysis of the efficacy data from these three pivotal trials included data from 559 patients who completed titration and were evaluated on a stable dose of levetiracetam and from 301 placebo-treated patients [16]. Overall, patients receiving levetiracetam had a 32.5% median decrease in the number of partial seizures per week, compared with a 7.0% decrease in the placebo-treated group ($P < 0.001$).

The percentage of patients who responded increased with increasing dose. Of patients receiving 1000, 2000, or 3000 mg/day, respectively, 27.7%, 31.6%, and 41.3%, had a 50% or greater reduction in seizures from baseline, compared with 12.6% of placebo-treated patients ($P < 0.001$ for each dose versus placebo). Only two (0.6%) patients in the placebo group became seizure-free, compared with 32 (5.7%) of those on levetiracetam ($P < 0.001$).

Levetiracetam as monotherapy

Success with an AED as add-on therapy is not considered sufficient to support its use as monotherapy. It is necessary to demonstrate that the drug is safe and effective when used as monotherapy in adequate and well-controlled clinical trials. The design and conduct of such trials is not

a simple matter, however. The Food and Drug Administration recommends comparison of the study drug to placebo in a randomized, double-blind clinical trial without the use of other, potentially confounding AEDs. However, according to the Committee for Proprietary Medicinal Products Note for Guidance on the clinical investigation of medicinal products in the treatment of epileptic disorders, therapeutic confirmatory monotherapy studies should always be randomized, double-blind, positive-controlled trials aiming to demonstrate at least a similar benefit/risk balance of the test product as compared with an acknowledged standard product at its optimal use.

The withdrawal from add-on therapy to monotherapy design is the first step recommended before conducting a confirmatory study in monotherapy. In this design, baseline AEDs are gradually withdrawn from patients selected at the end of the add-on period because their seizures were brought under adequate control in the course of the add-on trial [15]. If the frequency of seizures increases, or if adverse events become intolerable, patients are removed from the study. The primary efficacy outcome measure is time to exit or the percentage of patients who complete the monotherapy phase.

An early study making use of this design to evaluate levetiracetam as monotherapy for the treatment of patients with refractory partial seizures was the second European double-blind placebo-controlled trial discussed above [15]. Patients in this trial who had a reduction in partial seizure frequency of 50% or more in the 12-week add-on therapy phase were entered into an extension phase. In this phase of the study, patients were tapered off the baseline AED over a maximum of 12 weeks, after which they received 12 weeks of levetiracetam alone at the original dosage. At the conclusion of the add-on phase, 17 placebo patients and 69 levetiracetam patients were found to be eligible for the monotherapy phase. Of these 69 patients, 49 were successfully converted to monotherapy. Of these, 36 patients completed the study. Nine patients on levetiracetam monotherapy were seizure-free throughout the 12-week monotherapy period. The median percent reduction in partial seizure frequency compared with baseline was 73.8%. This study suggested that in patients with partial seizures not responding to standard AED treatment, levetiracetam can be successfully converted to monotherapy if the patient responds to levetiracetam as add-on therapy.

Several other reports of clinical success with levetiracetam as monotherapy have appeared as abstracts in the literature. Hovinga *et al.* [17] reported a retrospective review of the records of 77 adult and 27 pediatric patients treated with levetiracetam as add-on therapy. Eight adult patients and four children were converted to monotherapy. Seven of the adults and two of the children became seizure-free. In an open-treatment series reported by Krauss *et al.* [18], seven of 36 adult patients treated with levetiracetam achieved monotherapy. A chart review by Gustafson *et al.* found that of 50 children treated with levetiracetam for refractory epilepsy, eight became seizure-free, and four of these were successfully converted to monotherapy [19]. In another pediatric study, Mandelbaum *et al.* report that of 26 children with refractory seizures treated with levetiracetam, 24 remained on therapy at 3 months [20]. Of these, 12 had a greater than 50% reduction in seizure frequency, and six were seizure-free. Of the three on monotherapy, one was seizure-free.

Long-term experience

A review of long-term data on patients treated with levetiracetam showed that 54.1% were male and 86.5% were white [21]. The mean age was 37.9 years. The median daily dose was 3000 mg, and the mean duration of exposure to levetiracetam was 1044.9 days.

Few restrictions were placed on the antiepileptic management of these patients. Patients could be converted to monotherapy, additional AEDs could be added and subsequently removed, and the dose could be changed, all according to the clinical judgment of the investigators. Therefore, the data should be interpreted with caution, due to the limitation of selection bias. These data are however of clinical interest.

Sixty-seven patients were on monotherapy for at least 3 months at any given time during treatment with levetiracetam. Of these 67 patients, 49 were still on monotherapy at the end of the study. The analyses presented here are on these 49 patients. The demographic characteristics of this group are shown in *table 1*. The duration of monotherapy ranged from 132 to 1968 days; 67.3% were on monotherapy for 18 months to 4 years.

In this analysis, 67.3% of patients on monotherapy for at least 3 months completed the study. As shown in *table 1*, 2% discontinued due to adverse events and 6.1% discontinued due to lack or loss of efficacy.

Over the course of the long-term study, subjects in the monotherapy group had a very low seizure frequency per week and had a high likelihood of being seizure-free *(figure 1)*. This is consistent with clinical practice, where patients responding well to polytherapy will be selected for withdrawal to monotherapy. Seizure frequency remained stable in all cohorts, an indication of the sustained efficacy of levetiracetam.

Using survival analysis techniques, the probability of being seizure-free for at least 12 weeks was 64.2%. The probability of having a seizure-free period of at least 24 weeks (almost 6 months), at least 48 weeks (almost 1 year), and at least 156 weeks (almost 3 years) was 57.5%, 54.8%, and 52.2%, respectively. One subject was seizure-free for 276 weeks (about 5.3 years) when the study was terminated.

Table 1. Long-term experience with levetiracetam in subjects on monotherapy for at least 3 months at study end (*N* = 49)

Demographic characteristics	
Mean (SD) age, y	41.0 (14.4)
Male, *n* (%)	22 (44.9%)
White, *n* (%)	44 (89.8%)
Mean (SD) weight, kg	71.4 (17.9)
Mean (SD) body mass index, kg/m^2	24.7 (4.9)
Disposition of subjects	
ITT population	49 (100%)
Completed study	33 (67.3%)
Discontinued study	16 (32.7%)
Adverse event	1 (2%)
Lack/loss of efficacy	3 (6.1%)
Lost to follow-up	2 (4.1%)
Withdrawal of consent	5 (10.2%)
Other reason	5 (10.2%)
Adverse events	
Total no. of adverse events	365
Subjects with at least 1 adverse event	36 (73.5%)
Subjects with adverse events that led to discontinuation or dose reduction	3 (6.1%)
Subjects with treatment-related adverse events	15 (30.6%)
Subjects with serious adverse events	13 (26.5%)
Subjects with treatment-related serious adverse events	2 (4.1%)
No. of deaths	0

Table 2. Long-term experience with levetiracetam in subjects not on monotherapy for at least 3 months at study end (*N* = 456)

Demographic characteristics	
Mean (SD) age, y	37.7 (12.5)
Male, *n* (%)	251 (55%)
White, *n* (%)	393 (86.2%)
Mean (SD) weight, kg	72.8 (15.2)
Mean (SD) body mass index, kg/m^2	25.3 (4.5)
Disposition of subjects	
ITT population	456 (100%)
Completed study	241 (52.9%)
Discontinued study	215 (47.1%)
Adverse event	38 (8.3%)
Lack/loss of efficacy	135 (29.6%)
Lost to follow-up	8 (1.8%)
Withdrawal of consent	24 (5.3%)
Other reason	10 (2.2%)
Adverse events	
Total no. of adverse events	4169
Subjects with at least one adverse event	394 (86.4%)
Subjects with adverse events that led to discontinuation or dose reduction	95 (20.8%)
Subjects with treatment-related adverse events	228 (50%)
Subjects with serious adverse events	154 (33.8%)
Subjects with treatment-related serious adverse events	15 (3.3%)
No. of deaths	11 (2.4%)

In general, levetiracetam was very well tolerated. The types of adverse events were consistent with the known adverse event profile of levetiracetam.

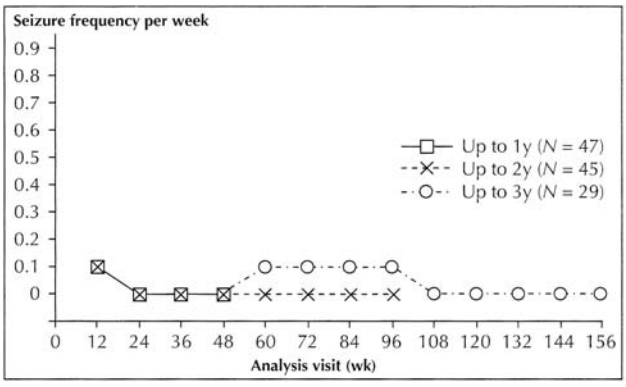

Fig. 1. *Mean total seizure frequency per week over the evaluation period by cumulative duration of exposure and analysis visit in patients on monotherapy.**
** The majority of the subjects included in this long-term database came from short-term studies. Because seizure frequency had already dropped during these short-term studies, seizure frequency in the long-term database was low from the beginning.*

The long-term database also included 456 patients who were not on monotherapy for at least 3 months at the end of the study. The demographic characteristics of this group were similar to those of the monotherapy group *(table 2)*, and 52.9% of patients completed the study. As in the monotherapy group, seizure frequency remained stable over time *(figure 2)*, an indication of the sustained efficacy of levetiracetam in this group as well.

The probability of being seizure-free for at least 12 weeks was 24.8%. The probability of having a seizure-free period of at least 24 weeks (almost 6 months), at least 48 weeks (almost 1 year), and at least 156 weeks (almost 3 years) was 20.1%, 17.6%, and 16.2% respectively. Two subjects were seizure-free for at least 300 weeks (about 5.8 years) and then left the study.

The adverse event profile in this group was also consistent with the known adverse event profile of levetiracetam.

Conclusions

The discovery and approval of many new AEDs in recent years has greatly increased the treatment options available to patients with refractory epilepsy. Most of the newer

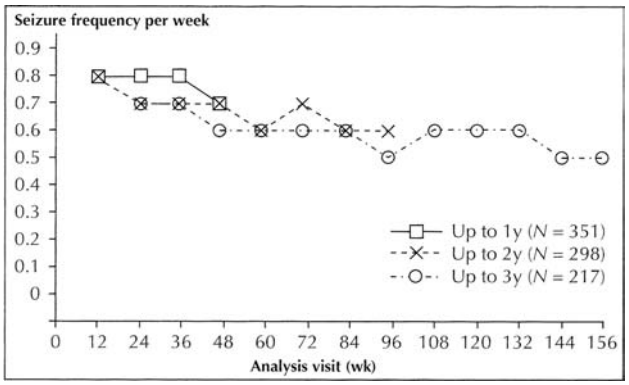

Fig. 2. *Mean total seizure frequency per week over the evaluation period by cumulative duration of exposure and analysis visit in patients not on monotherapy.**
** The majority of the subjects included in this long-term database came from short-term studies. Because seizure frequency had already dropped during these short-term studies, seizure frequency in the long-term database was low from the beginning.*

agents have been used as add-on drugs in clinical trials and medical practice. It has become clear, however, that monotherapy may be the treatment of choice for new-onset and refractory epilepsy, given the lower risk of adverse events and drug interactions [2].

The key difference between levetiracetam and other AEDs is its combination of efficacy, excellent tolerability, and ease of use. Recent studies have shown that levetiracetam demonstrates efficacy in many patients with refractory epilepsy as add-on therapy, and there is preliminary evidence for efficacy as monotherapy. Experience with levetiracetam monotherapy (up to 7 years) lends supportive evidence that levetiracetam monotherapy may be a safe, effective, and rational choice for the treatment of partial seizures.

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