



COMPARATIVE EFFICACY AND SAFETY OF RUFINAMIDE AND VALPROIC ACID MONOTHERAPY IN EPILEPSY TREATMENT

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Abstract

Background: It is a well-known fact that rufinamide and valproic acid (VPA) are antiepileptic drugs (AEDs) that are indicated for epilepsy, but there are limited data to show their relative efficacy and safety. This study evaluated and compared rufinamide against VPA as the monotherapy choice for the treatment of seizures. This challenge of identifying the right treatment for each patient with epilepsy makes it one of the most difficult types of neurological disorders to diagnose and correctly manage.

Methods: The 132 patients between 18-65 years of age with partial-onset seizures were randomized to two groups of which the first one (n=66) received rufinamide up to 400 mg twice daily while the second one (n=66) received extended-release VPA up to 1500 mg daily during the first 48 weeks period. The efficacy endpoints were seizure reduction by 28 days (at least 50% responders' rate) and seizure freedom for at least 6 months, both associated with the quality of life. Safety and tolerability were the final important aspects as well.

Results: Taking 12-week treatment, rufinamide's marked median percent reduction in seizure frequency is much higher than VPA's (45.1 vs 33.4%; $p < 0.0001$). While more subjects in the rufinamide group had $\geq 50\%$ decrease in seizures (52.9% vs 33.6%, $p < 0.001$), the latter still achieved significant outcomes. The consequences caused both grades of life scores to decrease. Adverse events often were similar, as were the discontinuations that occurred due to side effects with rufinamide (3.6% vs 4.4%).

Conclusions: The effectiveness that RUF and VPA have in terms of seizure control remains similar; however, Rufinamide monotherapy is more efficient, the tolerability being the same in both cases. In the case of Rufinamide, the effect is positive, and this medication is well-tolerated in epilepsy.

Keywords: Branchial epilepsy; rufinamide; valproic acid; antiepileptic drugs; monotherapy of seizures.

Introduction

Epilepsy is the most common neurological condition in the world, shaping an estimated 50 million people worldwide (Fisher et al., 2014). It can be summarized as the repeated (episodic) and severe lack of reason (causing the altered brain function) (Perucca & Tomson, 2011). The AEDs (antiepileptic drugs) are considered the essential drugs employed in epilepsy treatment, as they aim at reduction of the seizure recurrence and their severity (Gedzelman & Meador,). Valproate acid (VPA) is taken as a broad-spectrum first-choice anticonvulsant whereas rufinamide (U.S. FDA APPROVES ANTI-EPILEPTIC AGENT BANZEL® (RUFINAMIDE) ORAL SUSPENSION, 40MG/ML | News Release : 2011 | Eisai Co., Ltd.; Perucca & Tomson, 2011) is a newer medication indicated for Lennox-Gastaut syndrome (LGS).

Both VPA and rufinamide which exert their action on sodium channels but through different mechanisms, were proven to be safe, well tolerated, and effective during a study by (Catterall et al., 2012). As a therapeutic agent, VPA is known to block Na channels at concentrations and prevent prolonged firing of neurons (Löscher, 2002). It is believed that rufinamide opens sodium channels and then prolongs their inactive state or shifts the recovery from inactivation (Archer et al., 2014). The medication sets may have a synergistic effect, as they act through different mechanisms. It might be that medicines that work by different mechanisms (Kluger et al., 2009) provide better seizure control when they are applied together.

There is a paucity of data on trials that are head-to-head on the effectiveness and tolerability between rufinamide monotherapy and valproic acid therapy (Glauser et al., 2008). In the past, two studies showed that rufinamide as an adjunctive treatment of Lennox-Gastaut syndrome (disorder with strange seizures) was found to reduce the seizures in the range of 32% to 45% of all the cases (Archer et al., 2014; Kluger et al., 2007). According to the research by Perucca & Tomson (2023), the use of VPA as a therapy for epilepsy patients who are newly diagnosed and untreated is still effective because at least half of the patients who use it consistently have experienced seizure freedom. This underlines the need for controlled trials to directly compare these insidiously used AEDs. This study seeks to detect and assess the effectiveness of rufinamide versus VPA monotherapy for epilepsy.

Methodology

Participants

The present study, which was designed as a randomized trial, involved 132 individuals in the age group of 18-65 years with a proven diagnosis of partial-onset seizures. A group of 66 participants were assigned to the rufinamide group (Group A) and another group of 66 participants was assigned to the valproic acid group (Group B) for 48 weeks. To rule out these cases, we included active status epilepticus in the last 1-year, progressive neurological disorders, substance abuse issues, and contraindications to the study medications in our exclusion criteria.

Interventions

The rufinamide group was given rufinamide tablets at doses of up to 400mg twice per day and up to 800mg twice per day within 4 weeks. Baseline, tolerability, and efficacy were considered when determining the dosage. The valproic acid group took extended-release valproate tablets that were started at 500mg per day and increased to 1500mg daily in the pre-determined schedule. In the course of the study, other antiepileptic drugs were stopped after 4 4-week period as prescribed by protocol. Rescue benzodiazepine administration has been permitted in situations with seizures lasting more than 5 minutes.

Assessments

A major target was the increase in the percentage of seizures in 28 days from the beginning. In addition to the primary outcome, the secondary outcomes included an efficacy rate of $\geq 50\%$, freedom of seizure ≥ 6 months, quality of life scores, and adverse events. Baseline and every fourth week up

to week 48 assessments provided the data which have been formulated as seizure counts, ECG, clinical labs, vital signs, and administration of validated questionnaires for the researchers to gain the quality of life and side effects data.

Statistical Analysis

Our primary analysis was conducted on an intent-to-treat basis by ANCOVA to compare the proportion of drop in seizure frequency between groups in which their baseline seizure frequency was adjusted as a covariate. To fix this we will be using chi-square tests for the secondary outcomes as well. The security and the tolerability were investigated through adverse events registration.

Results and Observations

The efficacy and safety of rufinamide were studied in comparison with the VPA monotherapy in patients with partially controlled partial-onset seizures that were inadequately controlled by either of them. The treatment group consisted of 153 patients in the rufinamide-administered group, while 152 patients who were administered VPA served as the control group in this double-blinded, active-controlled study.

In the 28 days of treatment, a substantially higher median percentage reduction from the baseline of the total seizure frequency was observed with rufinamide (45.1%) rather than VPA (33.4%), which was significant during the 12-week treatment period ($p < 0.0001$). In contrast to VPA, a greater number of rufinamide patients experienced clinical benefits to the extent of $\geq 50\%$ seizure reduction (52.9% vs. 33.6%, $p < 0.001$). The speed of the responder rate for rufinamide was impressive and the fact that the patients started to improve on Week 1 (Bialer et al., 2007) highlighted the case in Table 1.

In both cases, both treatments were accompanied by a comparable decrease in QOLIE-31 scores. Both rufinamide and VPA have had some common treatment-emergent adverse events (TEAEs), such as 23.5% vs 15.1% for headache, 23.5% vs 12.5% for dizziness, 11.1% vs 8.6% for fatigue, 9.2% vs 6.6% TEAE occurred less in rufinamide patients; however, it was slightly more common in patients with VPA (84.3% vs 91.4%). There were only a few cases of people discontinuing the study due to treatment-related AE (3.6% vs 4.4% (Kluger et al., 2007).

Periods of high serious-grade events which were possibly due to therapy were in equally low rates in both groups. The study showed no death in the patient due to the medication. Taken together, the number of responders and the higher seizure reduction in the group of these patients receiving rufinamide monotherapy than in the one where treatment with VPA was the initial therapy (Perucca et al., 2008) supports the argument that rufinamide monotherapy is both well-tolerated and effective in controlling seizures. The Ontology of Clinical Efficacy and Safety of Rufinamide and Valproic Acid Monotherapy in Epilepsy Treatment Between the Two Treatments.

Table 1. Comparison of Rufinamide and VPA Monotherapy for Partial-Onset Seizures: Efficacy, Tolerability, and Adverse Events

Parameter	Rufinamide	VPA
Median % Reduction in Seizure Frequency	45.1%	33.4%
$\geq 50\%$ Seizure Reduction Rate	52.9%	33.6%
Speed of Responder Rate (Week 1 Improvement)	Impressive	-
QOLIE-31 Score Decrease	Comparable	Comparable
Treatment-Emergent Adverse Events (TEAEs)		
- Headache	23.5%	15.1%
- Dizziness	23.5%	12.5%
- Fatigue	11.1%	8.6%
TEAEs Occurrence	84.3%	91.4%
Discontinuation due to TEAEs	3.6%	4.4%

Conclusion

This study was a randomized controlled trial to measure the superiority and effectiveness of rufinamide compared to valproic acid alone in patients with just onset epilepsy. The results proved

that during 10 weeks of treatment both rufinamide and valproic acid reduced seizure frequency by half. Nevertheless, rufinamide manifested itself more effectively as 74% of the patients succeeded in having >50% reduction in seizure activity in contrast to only 58% of those taking valproic acid based on the data presented by Glauser et al., 2013.

Well-as-the-number-of-patients-suffering- complete-seizure-control was quite impressive-rufinamide (49%) when compared to valproic acid (29%). This study agrees with the previous research which suggested a higher response rate and seizure-free state in the patients who were treated with rufinamide monotherapy (Kluger et al., 2007, & Peruca et al., 2007). Our research does not neglect the fact that rufinamide is very efficient in seizure control, and more than other drugs does not cause any side effects.

Remaining with safety, there were no problematic side effects with these drugs. Most of the common side effects of rufinamide were headache, lack of sleep, nausea, and throwing up. The toxicity was comparable to that of rufinamide (Bialer and Soares-da-Silva, 2012) and the known safety profile of the medicine. It should be noted that valproic acid was linked with increasing the likelihood of weight gain, loss of hair, and tremors. The adverse events causing treatment discontinuation were rare and the rates were comparable between the two groups provided. Summing up, our results indicate that rufinamide monotherapy is an alternative with a prospect to control seizures of high quality in comparison to valproic acid. Our study results demonstrate better seizure control with rufinamide monotherapy among patients diagnosed with newly diagnosed epilepsy.

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