Neuropsychiatric Disease and Treatment

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REVIEW

Treating Lennox–Gastaut syndrome in epileptic pediatric patients with third-generation rufinamide

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
21 September 2010

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Abstract: Lennox–Gastaut syndrome (LGS) is a rare but debilitating pediatric epileptic encephalopathy characterized by multiple intractable seizure types. Treatment of LGS is challenging because of the small number of antiepileptic drugs (AEDs) which are effective for this syndrome, as well as the need for polytherapy in the majority of patients. This review focuses on the treatment of LGS with rufinamide, a recently approved third-generation AED with reported efficacy as adjunctive therapy for LGS. All relevant papers identified through a PubMed search on the treatment of LGS with rufinamide were reviewed. To date, the literature suggests improvements in seizure frequency for pediatric patients with LGS on rufinamide. Rufinamide appears to be especially effective for atonic or drop attack seizures. Rufinamide also displays a favorable adverse event profile compared with the older anticonvulsants, as well as a minimal number of drug interactions, making it a promising option for the adjunctive treatment of seizures associated with LGS.

Keywords: epilepsy, Lennox-Gastaut syndrome, pediatrics, seizure, rufinamide

Introduction

Lennox–Gastaut syndrome (LGS) is an uncommon but refractory epileptic encephalopathy of childhood, with a peak onset at 3–5 years of age.[1–3] It is classified by the International League Against Epilepsy as a symptomatic generalized syndrome and requires a triad of clinical characteristics for diagnosis.[4] First, patients exhibit an interictal slow spike-and wave pattern (less than 2.5 Hz) on the electroencephalogram with paroxysmal fast rhythms (10 Hz) during sleep. The second characteristic is multiple generalized seizure types. Tonic seizures (often during sleep), atonic or drop attack seizures, and atypical absence seizures are the most common types; however, patients may also exhibit myoclonic generalized tonic-clonic, partial absence, and unclassified seizures. The third characteristic is cognitive impairment, with severe mental retardation found in more than half of patients.[1,4–6]

LGS accounts for only 1%–4% of all childhood epilepsies, but is viewed as one of the most difficult epilepsies to control.[4] In many cases the etiology is unknown, and the presentation of multiple seizure types often leads to antiepileptic drug (AED) polytherapy.[7] The multidrug and high-dose regimens required increase the risk for drug interactions, thereby affecting adjunctive AED serum concentrations and increasing the risk of medication overdose or ineffective treatment. Moreover, most of the AEDs have intolerable adverse effects or can exacerbate different seizures which occur within LGS. Only a few AEDs have been shown to be effective for LGS.[8] Even with AED polytherapy, the long-term prognosis is poor, with a persistence of epilepsy in more than

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DOI: 10.2147/NDT.S6465

75% of patients.[9] This incomplete seizure control often results in significant lifetime health care costs for the patient.[10]

A patient's quality of life is very poor, with drop attacks being the most troubling presentation of LGS. These are the most physically damaging seizures, often causing head injuries due to falls.[11] Therefore, many patients require close supervision, protective headgear, or confinement. A reduction in drop attacks is one of the most clinically significant outcomes for patients with LGS.[12]

The treatment goals for LGS are to provide the best seizure control possible using the fewest medications, while limiting the risk of adverse events.[13,14] Currently, valproic acid is considered first-line therapy, and is considered effective for multiple seizure types in LGS; however, its use is not supported by controlled trials. Furthermore, the risk of life-threatening hepatotoxicity appears to be greater in children under two years of age, and valproate consequently tends to be avoided in this subgroup if other options are available.[15] Topiramate, lamotrigine, and felbamate have demonstrated efficacy as adjunctive therapies in randomized, placebo-controlled trials.[16–18] Topiramate and lamotrigine are currently recommended as second-line therapy and have comparatively more favorable tolerability.[15,19] Felbamate lacks sedative effects, but it also carries serious risks of aplastic anemia and hepatotoxicity which limit its use.[19] Clobazam, a benzodiazepine with less sedative potential than other members of its class, is also a potential adjunctive treatment.[20] Other treatment options include zonisamide, a ketogenic diet, vagus nerve stimulation, or corpus callostomy.[15,19]

Due to the limited success of treatments for LGS, there is still a great demand for novel medications to manage this syndrome. An ideal medication would be effective in reducing the multiple seizure types associated with LGS, have a tolerable side effect profile, and have limited drug–drug interactions with other AEDs.

The antiepileptic efficacy and tolerability of rufinamide was established in a clinical trial which led the United States Food and Drug Administration (FDA) to grant it orphan drug status in 2004. Rufinamide then received FDA approval in early 2009 for adjunctive treatment of seizures associated with LGS in patients four years and older, as well as for adjunctive treatment of partial seizures in adults and adolescents. The purpose of this review is to analyze the current literature describing rufinamide use for the treatment of LGS.

Methods

A PubMed search was conducted by the authors for available studies limited to the terms "rufinamide" and "Lennox-Gastaut syndrome". Study population were evaluated for pediatrics and review article references were compared to search results.

Rufinamide

Rufinamide [1-(2,6-difluoro-phenyl)methyl-1H-1,2,3-triazole-4-carboxamide], Banzel® (Eisai Co., Woodcliff Lake, NJ) is a third-generation AED with a triazole structure that has some similarity to lamotrigine.[21] It mainly acts by prolonging the inactive state of sodium channels, inhibiting the firing of sodium-dependent action potentials.[22]

Pharmacokinetics/pharmacodynamics

Rufinamide is a lipophilic compound manufactured as 200 mg and 400 mg coated tablets.[23] A suspension is not currently available; however, a study of extemporaneously compounded suspensions of rufinamide (40 mg/mL) in a 1:1 mixture of Ora-Plus® and Ora-Sweet® or Ora-Sweet SF® were found to be stable for at least 90 days.[24]

Rufinamide is not soluble in water and dissolves poorly in gastric contents. In a study of three healthy adult volunteers, a 600 mg oral dose was extensively absorbed (≥85%).[25] Absorption is believed to be dissolution rate-limited and takes place in the small bowel.[26] The maximum plasma concentration (mean) was reached within 6.6 hours after a single 400 mg dose.[27] In three studies analyzing the influence of food on absorption in healthy adult subjects, taking rufinamide within one hour from mealtimes did not significantly affect plasma concentrations. However, bioavailability is significantly increased with administration after a high-fat meal versus administration after prolonged fasting. Prolonged fasting may decrease plasma levels and decrease seizure protection.[26] Administration with food is recommended .[23]

Rufinamide is approximately 34% bound to plasma proteins.[26] It is extensively metabolized to a carboxylic acid derivative (CGP 47292) and to glucuronide conjugates of CGP 47292. Very small amounts of the parent drug are found in the urine and feces. About 85% of the drug is eliminated renally. Rufinamide is not believed to be metabolized via the cytochrome P450 system.[27,28] It displays monoexponential elimination, with a mean half-life of about nine hours in adults.[27]

A population analysis in 117 children (4–11 years) and 99 adolescents (12–17 years) determined that the pharmacokinetics of rufinamide were similar to those seen in adult studies.[23] In a pharmacokinetic study of 129 adults and children with LGS, a decrease in bioavailability was observed with higher doses in the children. Clearance is also proportional to body surface area; therefore, children display higher steady-state concentrations and lower clearance compared with adolescents or adults.[29]

Rufinamide has a low potential for drug–drug interactions due to its lack of protein binding and metabolism independent of the cytochrome P450 system. This lack of significant drug interactions has been demonstrated clinically through a pharmacokinetic analysis using data from five double-blind studies in adults and children.[30] Rufinamide was coadministered with carbamazepine (n = 903), valproic acid (n = 588), lamotrigine (n = 200), phenytoin (n = 299), phenobarbital (n = 149), and topiramate (n = 69). Rufinamide did not affect the clearance of topiramate or valproate, but increased the clearance of carbamazepine and lamotrigine, and decreased clearance of phenobarbital and phenytoin. However, these interactions were not considered clinically significant.[30] Another study demonstrated that rufinamide concentrations increased with concomitant valproate by 40% and 11% in children and adults, respectively. Therefore, dose reduction may be required with the initiation or withdrawal of concomitant valproate.[29] Rufinamide also resulted in a small increase in the clearance of the oral contraceptive Ortho-Novum® (ethinyl estradiol and norethindrone); however, the clinical significance of this interaction has not been elucidated.[31]

Safety

In a randomized, double-blind, placebo-controlled trial of rufinamide in 138 children and adults with LGS, the majority of reported adverse effects were similar between placebo and rufinamide at a dose of 45 mg/kg. There were significant differences in somnolence (24.3% with rufinamide versus 12.5% with placebo) and vomiting (21.6% with rufinamide versus 6.3% with placebo).[14] Cognitive or psychiatric adverse events occurred in a lower percentage of patients taking rufinamide (17.6%) versus placebo (23.4%).[14] Polytherapy increased the risk of adverse effects. During the extension phase of this trial, a total of 113 (91.1%) patients experienced an adverse effect. The most commonly reported adverse effects were vomiting (30.6%), pyrexia (25.8%), upper respiratory tract infection (21.8%), and somnolence (21%). A total of 82 patients discontinued the medication prematurely, 9.7% due to adverse effects.[32] The relationship between serum drug concentrations and adverse effects has also been analyzed in 1398 patients from both controlled and clinical studies. The most common adverse effects reported in controlled, double-blind pediatric studies were dizziness (13%), fatigue (17%), nausea (9%), vomiting (7%), diplopia (6%), and somnolence (7%).[26,33] Adverse effects were reported in a slightly higher percentage of adults (versus children), those with increased body weight, and in females. Increasing rufinamide plasma concentrations was also associated with an increase in adverse effects.[33]

A pooled analysis of seven clinical studies examined the incidence of adverse events specifically in the pediatric population (212 rufinamide-treated pediatric patients aged 3–16 years, 197 placebo-treated patients aged 4–17 years, and 391 patients in both double-blind or open-label extensions).[34] Overall, for all studies, 391 patients received an average dose of 41.67 mg/kg/day for 12–24 months. The most commonly reported adverse events were vomiting (26.3%), headache (22.5%), and pyrexia (18.7%).[34] The most common serious adverse effects that occurred in more than one patient were aggravated seizures (2.8%), status epilepticus (2%), pneumonia (2%), and vomiting (1.5%). Discontinuation of treatment occurred in 12.5% due to adverse effects. Five possible cases of AED hypersensitivity syndrome was discovered retrospectively in children younger than 12 years and within the first four weeks of treatment. In the double-blind trials alone, the median dose of rufinamide was 41.96 mg/kg/day for an average duration of three months. The most common adverse events reported (rufinamide versus placebo) were somnolence (17% versus 8.1%), vomiting (16.5% versus 7.1%), and headache (16% versus 8.1%). Clinically relevant decreases in weight (≥7%) were seen only in the rufinamide group (11/188, 5.9%) versus an increased incidence of weight gain observed in the placebo group (15/178, 8.4%). The rates of psychiatric adverse events that occurred between rufinamide and placebo were comparable, at 10.4% versus 14.2%, respectively. Only one patient exhibited QT prolongation and another exhibited electrocardiographic changes (exact change not specified).

In 18 healthy volunteers treated for 18 days with rufinamide, dose-dependent QT interval decreases were reported.[35] Rufinamide is therefore contraindicated in patients with a short QT interval due to risk of short QT syndrome (syncope, ventricular arrhythmia, possible sudden death).[35] Obtaining an electrocardiogram prior to initiating rufinamide would be prudent.

Efficacy in Lennox–Gastaut syndrome

Several trials have evaluated the effectiveness of rufinamide as an adjunctive treatment in LGS (see Table 1). The efficacy of rufinamide as an adjunctive therapy for LGS was evaluated in a multicenter, randomized, placebo-controlled, parallel-group study in 138 patients aged 4–37 (mean 14) years of age.[14] This study included a 12-week, double-blind

Table 1 Trials of rufinamide for Lennox–Gastaut syndrome in pediatric patients

Study	Population	Design	Results
Glauser et al[14]	138 patients Age 4–37 years Mean age 14.1 years Patients diagnosed with LGS, having ≥90 seizures in month prior to entry, and receiving stable treatment with 1–3 concomitant AEDs	12-week, randomized, double-blind, placebo-controlled, parallel-group Subjects randomized to rufinamide up to 45 mg/kg/day (14 days titration) or placebo in addition to other AEDs	Median percent change in total seizure frequency per 28 days versus placebo: –32.7 versus –11.7, $P = 0.0015$ Median percent change in tonic–atonic seizure frequency per 28 days versus placebo: –42.5 versus 1.4, $P < 0.0001$ Improvement in seizure severity from parent/guardian global evaluation versus placebo: 53.4 versus 30.6, $P = 0.0041$ Most common adverse effects were somnolence (24.3% versus 12.5%), vomiting (21.6% versus 6.3%), pyrexia (13.5% versus 17.2%), and diarrhea (5.4% versus 10.9%) Six discontinuations due to adverse events (3 vomiting, 2 somnolence, 2 rash)
Glauser et al[32]	124 patients from previous study treated for a median of 432 days at 10–45 mg/kg/day Continued to meet all relevant inclusion/exclusion criteria from blinded study	Open-label extension phase 14-day conversion period	There was a decrease in seizure frequency observed at all time points up to 3 years. Overall 50% response rate was 36.9%, with a 44.4% reduction in tonic–atonic seizures. These reductions were consistent over time. In approximately 50% of patients, the total daily dose of concomitant AEDs was decreased over 30 months of adjunctive treatment. 113 patients (91.1%) experienced an adverse effect; 12 patients discontinued rufinamide due to adverse effects.
Kluger et al[36]	45 children and 15 adults (34 males, average age 14.5 years) taking concomitant antiepileptics	12-week, observational, retrospective data collection from eight epilepsy centers in Germany and Austria Initial dosing/titration at the discretion of the physician, most started out at 10 mg/kg/day	The mean final dose of rufinamide was 35.6 mg/kg/day. In the analysis of a subgroup of 31 patients with LGS, 54.8% (17/31) had a response rate, defined as a greater than 50% reduction in seizure frequency. Four patients were seizure-free. 35 (58.3%) patients in all subgroups experienced at least one adverse event. Mild fatigue, vomiting, and anorexia were observed in 10%–18% of patients. No serious adverse events were reported. A total of eight patients (13.3%) discontinued rufinamide during the three-month observation period (four due to adverse events).

phase followed by an open-label extension phase. Patients were randomized to placebo or twice-daily oral rufinamide titrated over 7 to 14 days to a daily target dose of 45 mg/kg in addition to their maintenance regimen. Of note, this trial set a detectable level of significance at 0.025. The two groups, placebo (n = 64) and rufinamide (n = 74), were equally distributed demographically except for a slightly higher age and weight in the rufinamide group. Valproic acid, lamotrigine, and topiramate were the most common concomitant medications. Rufinamide serum concentrations ranged from 4.95 to 48.15 μg/mL. The median reduction from baseline in the frequency of drop attacks per 28 days was significantly greater for rufinamide versus placebo (−42.5% versus +1.4%, $P < 0.0001$). Absence seizures showed a statistically significant decrease as well. The median reduction from baseline in frequency of all seizures was also significantly greater for study medication versus placebo (−32.7% versus −11.7%, $P = 0.0015$). These results were associated with a greater proportion of responders (patients achieving ≥50% reduction in seizures per 28-day period) for rufinamide versus placebo. The responder rate for total seizures was 31.1% versus 10.9% and for drop attacks was 42.5% versus 16.7% for rufinamide versus placebo, respectively. No patients were determined to be seizure-free during the study. However, 4.1% of patients demonstrated a 100% reduction in tonic–atonic seizures. A significant difference related to the parent/guardian global evaluation of the patient's condition at the end of the study was not demonstrated either. There were no significant differences compared with placebo in the incidence of adverse events, apart from somnolence and vomiting, which was higher in the rufinamide group.

Following completion of this study, 123 patients (including 74 males) entered the open-label, treatment-extension phase with a median dose of 1800 mg/day for a median duration of 432 days.[32] Sixty percent of patients were treated for more than 18 months, 40% for more than two years, and 12% for three years or longer. Approximately half of the patients decreased their total daily dose of concomitant AEDs during 30 months of adjunctive therapy with rufinamide. The reduction in median total seizure frequency was maintained, with some improvement noted in patients who continued treatment for up to three years. The responder rate for all seizures was also maintained, with 36.9% of patients having a 50% decrease in seizure activity during the open-label phase. In addition, 21.3% of patients achieved a ≥75% reduction in overall total seizures, with 29.1% of patients achieving a ≥75% reduction in tonic–atonic seizures.

The long-term results of rufinamide in an open-label extension trial (trial presented above) were also published by the same research group.[36] Kluger et al observed patients from 10 to 1149 days, with a median of 432 days. After study termination had occurred (44 months), 33.9% of patients were still receiving rufinamide, whereas 66.1% had discontinued due to various reasons, including unsatisfactory therapeutic response (n = 51), adverse events (n = 12), or other unspecified reasons (n = 19). Notably, patients who had been receiving placebo (n = 59) during the double-blind treatment phase went from a 1.5% decrease in total seizure frequency to a 22% median reduction in total seizure frequency after two weeks on rufinamide. During the last 12 months of rufinamide treatment, response rates (≥50%) for total seizures and for tonic–atonic seizures were 41% and 47.9%, respectively. Eight patients (6.8%) achieved seizure freedom within the last 12 months of rufinamide treatment. More serious adverse events were reported during the extension study (13.7%) compared with the double-blind study (2.7%). Serious adverse events reported and suspected to be treatment-related included rash, constipation, esophagitis, decreased weight, gastritis, anorexia, vomiting, lethargy, and status epilepticus. This trial demonstrated that rufinamide was able to maintain seizure control over the long term.[36]

A 12-week, retrospective, observational study conducted in Europe by Kluger et al included 45 children and 15 adults (mean age 14.5 years) with various refractory epilepsy syndromes.[37] Thirty-one of the study patients were diagnosed with LGS. Researchers determined response rates by comparing frequency of seizures during the first four-week period of the trial before drug initiation versus seizure frequency with rufinamide during the last four weeks of observation. Seventeen patients with LGS responded to rufinamide (54.8%), with eight patients exhibiting a 50%–75% seizure reduction, five a 75%–99% reduction, and four achieving complete freedom from seizures during the last four weeks of observation.[37]

Other studies

A three-year cost-efficacy analysis of rufinamide versus lamotrigine and topiramate for children with LGS was conducted in the United Kingdom based on the current published literature.[38] This study looked at the relationship between costs and quality of life years. Quality of life was based on response rates to each medication, as well as tolerability. Rufinamide had the highest cumulative cost compared with topiramate and lamotrigine. However, the authors concluded that the extra expense for rufinamide was warranted if a patient's quality of life was improved, because LGS can be such a devastating condition.

Currently, there are no direct comparisons of trial data for rufinamide versus other adjunctive therapies for LGS. In addition, a Cochrane review of LGS treatment was unable to compare rufinamide effectively as an adjunctive therapy to other AEDs due to a lack of direct comparison trials, as well as differences in trial designs and population.[39] This review did suggest, however, that one specific medication has not been shown to be more effective than another and, thus, rufinamide, lamotrigine, topiramate, and felbamate should all be considered as an adjunctive treatment for LGS. Patient-specific issues may assist with guiding selection of medication. Rufinamide may be a more efficacious option compared with current alternatives due to the fact that the patients included in the relevant clinical studies may have had more refractory forms of LGS and were already taking multiple AEDs.

Conclusion

The available literature to date examining rufinamide, a third-generation AED, for the treatment of LGS suggests that it is both a safe and effective adjunctive treatment option for patients who are refractory to therapy with multiple AEDs. The FDA-approved pediatric dosage is up to 45 mg/kg or 3200 mg/day divided into two doses, which is consistent with effective dosages from the trials. Tablets may be crushed for pediatric administration and the dose should be administered with a meal to increase absorption.[23] Cost may be a challenge due to the availability of only brand-name dosage forms on the market. However, a pharmacoeconomic analysis[38] suggests that increased quality of life with rufinamide outweighs its increased cost compared with alternatives.

The most common adverse effects for rufinamide include somnolence, vomiting, dizziness, and fatigue, but these are relatively mild and typically do not warrant drug discontinuation.[33] Rufinamide is a worthwhile adjunctive treatment for LGS due to its relative lack of clinically significant drug interactions and its acceptable adverse effect profile compared with older anticonvulsants. Additional studies are needed to further assess its short- and long-term efficacy and safety, as well as drug interactions. In addition, a direct comparison between rufinamide and alternative adjunctive treatments is warranted to assess its place in therapy. Rufinamide is a promising adjunctive agent for the treatment of pediatric LGS and may significantly decrease seizure frequency in patients who are refractory to other therapies.

Disclosure

The authors report no conflicts of interest in this work.

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