

Update on the management of Lennox-Gastaut syndrome with a focus on rufinamide

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Objective: This review summarizes the treatment of Lennox-Gastaut syndrome, an intractable epileptic encephalopathy of early childhood. In particular, the review focuses on rufinamide, a recently released anticonvulsant medication with reported effectiveness in this epilepsy syndrome.

Methods: A systematic literature search (PubMed) was performed to review the existing literature pertaining to the treatment of Lennox-Gastaut syndrome as well as studies involving rufinamide as an anticonvulsant medication.

Results: The published literature to date documents a beneficial effect of rufinamide on children over 4 years old with Lennox-Gastaut syndrome. Studies indicate a significant decrease in tonic and atonic seizure frequency as well as total seizure frequency compared to placebo-treated children. Rufinamide appears to be well tolerated and a safe medication, somnolence and vomiting being the most common side effects.

Conclusions: Rufinamide is a promising adjunctive therapy for Lennox-Gastaut syndrome, an intractable childhood epilepsy. To ensure its optimal effectiveness, clinicians must be familiar with the medication's clinical response profile and potential for adverse effects.

Keywords: pediatric, epilepsy, epileptic encephalopathy, Lennox-Gastaut syndrome, rufinamide

Introduction – Lennox-Gastaut syndrome and its treatment

Lennox-Gastaut syndrome (LGS), one of the catastrophic epilepsies of childhood, is classified by the International League Against Epilepsy as a symptomatic generalized epilepsy syndrome. Originally described in 1966, this “epileptic encephalopathy” requires 3 components for diagnosis.¹⁻⁴ First, children must exhibit multiple seizure types. Tonic seizures (especially during sleep), atonic (astatic or drop attacks) seizures, and atypical absence seizures are most commonly observed; some patients also develop myoclonic, generalized tonic-clonic, or partial seizures. Nonconvulsive status epilepticus is quite frequent, occurring in over 50% of LGS patients. The second feature required by the definition is an interictal awake electroencephalogram (EEG) pattern consisting of slow spike wave discharges (less than 3 Hz), usually with a generalized distribution. Another characteristic EEG feature is paroxysms of low voltage fast activity at about 10 Hz during sleep. The third component of the definition of LGS is cognitive impairment involving moderate to severe mental retardation and behavioral disorders including aggression and autistic features.

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Over 75% of children with LGS have an identifiable cause (symptomatic or presumed symptomatic/cryptogenic). These include numerous congenital or acquired etiologies, such as cortical maldevelopment, perinatal hypoxia-ischemia, CNS infection, or neurometabolic disorders. About 20% of children with LGS have prior infantile spasms (West syndrome) and evolve into LGS with age. The typical age of onset of LGS is between 2 and 5 years; boys are affected about 5 times more often than girls.⁵ The prognosis of LGS is poor, with regard to both seizures and cognitive outcome. Risk factors for a poor cognitive prognosis include symptomatic etiology, history of nonconvulsive status epilepticus, prior infantile spasms, and early age of seizure onset.⁶

Due to the encephalopathic nature and multiple seizure types, LGS is notoriously difficult to treat.⁷ Many drugs reduce seizures initially, only to lose effectiveness over time. Children often end up on polypharmacy with numerous anticonvulsants, which adds to the cumulative side effects and drug–drug interactions.³ Furthermore, the seizures themselves are thought to contribute to the cognitive impairment and behavioral comorbidities.

Difficulties in diagnosing LGS are discussed in detail in a recent review.⁴ Sometimes the classic clinical and EEG features are not present at the onset of the syndrome. Due to the heterogeneous causes, the diagnosis may be delayed or uncertain, at least initially. Some aspects of the seizure semiology can be confusing. For example, it can be difficult to differentiate between spasms and tonic seizures and to identify and quantify atypical absence seizures accurately. Some rapidly secondarily generalized seizures can also mimic seizure types seen in LGS.

Many treatment attempts in LGS are anecdotal and empirical. Systematic difficulties complicate performance of drug trials in LGS, including the very frequent occurrence (often nearly uncountable) of atypical absence seizures, the inaccuracy of parental reports of seizure semiology and frequency, the wide range of etiologies, and the evolution of seizure types over time.

A few randomized, double blind, placebo-controlled trials of single agents have been performed in LGS.^{5,7} Felbamate,⁸ lamotrigine,⁹ and topiramate¹⁰ reduced the occurrence of atonic and tonic-clonic seizures in children with LGS. All of these studies entailed addition of the study drug to other medications, and the studies varied considerably in their experimental design and patient selection criteria. No head-to-head trial comparing more than one drug has been published.

Even with the new generation of anticonvulsants, valproic acid is considered the most useful initial medication of choice

for drop attacks, atypical absences and myoclonic seizures in LGS.^{5,11,12} Although there are no controlled studies, valproic acid is reportedly effective against multiple LGS seizure types including atypical absence, myoclonic, and other situations in which slow spike-wave discharges are found on EEG. Caution must be exercised in using valproic acid in children under the age of 2 years, especially if they are receiving several other anticonvulsants, because of the risk of hepatotoxicity. In that age group, it has been recommended to try topiramate or lamotrigine first.¹¹ Felbamate could also be considered as an alternative to valproic acid, because felbamate lacks the sedative side effect seen with other anticonvulsants (eg, topiramate, benzodiazepines), which exacerbates seizure occurrence. Owing to the risk of aplastic anemia and hepatotoxicity with felbamate use, this medication must be used with caution and appropriate patient monitoring of blood levels, liver function, and hematologic indices. Caretakers must be provided detailed information about the potential risks of felbamate. The effects of benzodiazepines are variable. A recent study showed that clobazam significantly reduced both drop and non-drop seizures in a dose-dependent manner in patients with LGS.¹³ Clobazam reportedly has less sedative effects than other benzodiazepines, making it an attractive potential adjunctive treatment for LGS.

An animal model of LGS does not exist, hampering progress in design of therapeutics. It is not surprising that there is no experimental model, since LGS comprises so many distinct seizure types and lacks a consistent underlying etiology. Treatment of rats with a cholesterol synthesis blocker produces atypical absence seizures with slow spike waves, providing an opportunity to study the mechanism of this specific seizure type, which appears to involve GABA_B receptors.¹⁴ These observations have not yet been exploited therapeutically.

Some general treatment considerations include recommendations to use as few anticonvulsants concurrently as possible to avoid side effects from polytherapy, avoid excessive drowsiness which exacerbates several of the seizure types in this syndrome, and consider the cognitive and psychological comorbidities which result from both LGS and its treatment. Clearly, a multidisciplinary approach is required to address the medical and psychosocial aspects of LGS. At present, authorities recommend valproic acid as the first line medication, followed by one or two of the second-line agents (lamotrigine, rufinamide, topiramate, clobazam, felbamate, levetiracetam).^{5,12} If those therapies fail to achieve treatment goals, zonisamide, the ketogenic diet, vagus nerve stimulation, or corpus callosotomy can be tried

(the latter targeting drop attacks). Of note, carbamazepine and gabapentin can exacerbate some of the seizure types in LGS.^{11,15} The role of newer anticonvulsants such as vigabatrin and zonisamide remain undetermined in LGS.

Rufinamide

Rufinamide [1-(2,6-difluoro-phenyl)methyl-1*H*-1,2,3-triazole-4-carboxamide] is a triazole derivative granted orphan drug status for the adjunctive treatment of LGS in the United States in 2004. It was released for use in Europe in 2007. In January 2009, rufinamide was approved by the United States Food and Drug Administration for treatment of LGS in children 4 years of age and older. It is also approved for adjunctive treatment of partial seizures in adults and adolescents.¹⁶ Rufinamide is structurally unrelated to other anticonvulsants. Its mechanism of action reportedly involves decreased firing of high frequency sodium-dependent action potentials and prolongation of sodium channel inactivation.¹⁷ Enhancing sodium channel inactivation would prevent a neuron from generating subsequent bursts of high frequency action potentials. However, data implicating an effect of rufinamide on sodium channels is presently published only in abstract form and, given the preclinical profile, other mechanisms of action are likely to operate.¹⁸ Rufinamide has a wide spectrum of anticonvulsant effectiveness in animals including the maximal electroshock model (for generalized tonic-clonic and partial seizures) and the subcutaneous pentylenetetrazol model (for clonic seizures).¹⁹ In support of the hypothesized action of rufinamide on sodium channels, seizure protection in those *in vivo* models is also afforded by other anticonvulsants that block sodium channel function. Rufinamide also blocks seizures induced by subcutaneous strychnine, bicuculline, and picrotoxin.²⁰

Rufinamide has an excellent safety profile in animals and lacks obvious cognitive side effects and behavioral toxicity at clinically relevant doses. On the rotorod test of motor coordination, rufinamide had a higher safety index than phenytoin, phenobarbital, and ethosuximide.¹⁹ The drug also appears to be relatively devoid of cognitive side effects in humans. In a multicenter study of 189 adolescent and adult patients with partial seizures, 12 weeks of treatment with rufinamide failed to cause deficits (compared to placebo) in several measures of cognitive function, including psychomotor speed and alertness, processing speed, and working memory.²¹

Pharmacokinetics

Taken orally, rufinamide is well absorbed (~85% after an oral dose).²² The absorption rate is slow and the extent of

absorption decreases as the dose is increased. After a single 400 mg oral dose in healthy adults, the time to maximum plasma concentration ranges from 1.5 to 10 hours with an average of about 6 hours, with a mean maximum plasma concentration (C_{max}) of 3.03 $\mu\text{g/mL}$.²³ Rufinamide has low protein binding (~34%) and food does not affect the time to maximum plasma concentration or peak plasma concentration.²² The plasma half life is 6 to 10 hours and is unaffected by renal disease. There is no reported effect of age on the half-life of rufinamide.

Rufinamide is eliminated primarily via metabolism, the principal metabolite being a carboxylic acid derivative. This metabolite primarily appears in the urine, and only about 2% of rufinamide occurs in the urine unchanged. The metabolite has no known pharmacological activity. The cytochrome P450 system is not involved.

Drug–drug interactions

The low plasma binding rate of rufinamide suggests that drug–drug interactions are likely to be minimal. However, in conditions like LGS, in which polypharmacy is usual, careful elucidation of drug–drug interactions is necessary. In all of the clinical trials with rufinamide, patients were on multiple anticonvulsants. In the largest trial of rufinamide in LGS, there were no significant effects of rufinamide on the plasma concentrations of valproic acid, lamotrigine, or topiramate.²⁴ There is no study of the effects of rufinamide on felbamate concentration.

At average steady state concentrations of rufinamide, the pharmacokinetics of several other anticonvulsants were not significantly affected. This comparison includes population pharmacokinetic analyses of carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproic acid. However, phenytoin clearance was decreased at average steady state levels of rufinamide up to 21%, suggesting that phenytoin levels should be closely monitored in patients on concurrent rufinamide.

The clearance of rufinamide is not significantly affected by several other anticonvulsants including carbamazepine, phenytoin, primidone, and phenobarbital. However, rufinamide clearance was decreased by valproic acid with elevated rufinamide levels of up to 70%.²⁰ Therefore, valproic acid therapy should be introduced cautiously and at relatively low doses in children already on rufinamide.

Efficacy studies

Results from randomized controlled clinical trials of rufinamide are just appearing. Early sponsored studies, including

open label extensions, provided data that rufinamide had a beneficial effect as add-on therapy for partial seizures in adolescents and adults. For LGS, a single double-blind randomized placebo controlled trial has been published.²⁴ This study involved 138 patients between the ages of 4 and 30 years who had LGS diagnoses for a median of 7.5 years. About one-third of participants were under 12 years of age.

Study subjects were randomized to either oral rufinamide (titrated up to 45 mg/kg/day over 14 days) (N = 74) or placebo (N = 64) in addition to their other antiepileptic drugs. This study involved a 28-day baseline followed by an 84-day parallel group treatment (14 days titration, 70 days maintenance). Primary end points were the percent change in seizure frequency and the parent/guardian ratings of seizure severity.

The investigators found a significant decrease in total seizures compared with placebo (−32.7% vs −11.7%; $P = 0.0015$), and tonic-atonic seizures compared with placebo (−42.5% vs +1.4%; $P < 0.0001$). The patients on rufinamide also had a greater improvement in seizure severity and a higher 50% responder rate compared with placebo for both total seizures and tonic-atonic seizures. Adverse effects in this study were modest, with 24% of treated patients experiencing sedation and 21% experiencing vomiting. Eight percent of the rufinamide group withdrew because of adverse side effects. Cognitive or psychiatric adverse events were less common among rufinamide-treated patients than in the placebo group. It was concluded that rufinamide is well tolerated and efficacious for seizures in LGS.

A 3-year open-label followup study, published in abstract form only, reports continued rufinamide effectiveness.²⁵ That study included 124 patients treated for a median of 432 days at a dose of 10 to 45 mg/kg/day. Compared to the placebo group, there was a decrease in total seizures at all time points assessed up to 3 years, ranging from −42.6% to −79.3%. Furthermore, rufinamide was well tolerated over the long term, with only 12 patients discontinuing the drug because of adverse side effects (most commonly vomiting, pyrexia, and somnolence).

A recently published study from Europe, using observational retrospective data from multiple centers, examined the effectiveness of rufinamide in children and adults with refractory epilepsy, including LGS.²⁶ In the subgroup with LGS, 17 of 31 patients (55%) had a response rate with greater than 50% reduction in countable seizures. Investigators found fatigue, vomiting, anorexia in 10% to 20% of patients but no serious adverse effects. Again, this study concludes that rufinamide is effective and well tolerated in patients with refractory epilepsy, including LGS.

Although promising as a novel anticonvulsant in LGS, several caveats arise regarding rufinamide. In part, issues relate to the study populations. As discussed above, patients with LGS are notoriously difficult to treat, are often treated with multiple anticonvulsant medications, and seizures are of several different types and difficult to monitor and count. Therefore, the question arises as to what place rufinamide will hold in overall treatment algorithm for LGS. The drug is promising with good effectiveness and tolerability studies to date. However, a larger number of patients must be treated with this medication to establish its role in the treatment armamentarium. There are no head-to-head studies comparing rufinamide with other anticonvulsants. The role of this new medication in relationship to prior drugs with some reported effectiveness in LGS needs to be further defined.

Conclusions

Rufinamide is a novel, broad-spectrum anticonvulsant drug with promising potential for treatment of many seizure types. In particular, the multiple seizure types seen in patients with LGS may be amenable to treatment with rufinamide. Rufinamide appears to have a good safety profile and is well tolerated with minimal expected side effects. Some of the most common side effects (eg, somnolence, vomiting) could perhaps be ameliorated by slow titration. Patient and caretaker satisfaction data need to be obtained. Given the devastating nature of the seizures and cognitive impairments in LGS, any treatment with an even modest benefit is a welcome addition to the therapeutic armamentarium.

Disclosure

The author declares no conflicts of interest.

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