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Rufinamide: Use in Patients with Refractory Epilepsy or Lennox Gastaut Syndrome

Marcia L. Buck, Pharm.D., FCCP

Lennox-Gastaut syndrome (LGS) is a rare form of epilepsy consisting of multiple seizure types, including tonic-atonic "drop attacks," and cognitive impairment. Many patients with LGS require a multi-drug regimen, with antiepileptics such as valproic acid, lamotrigine, or topiramate, as well as corticosteroids or immune globulin. Additional therapies have included a ketogenic diet, vagus nerve stimulation, and surgical resection. Despite an aggressive approach to treatment, many patients continue to have frequent seizures.[1,2]

Several new agents have been under investigation over the past decade which may be useful in patients with LGS.[1,2] In 2004, rufinamide was granted orphan drug status in the United States and Europe.[1] It was approved as a prescription drug by the Food and Drug Administration (FDA) on November 14, 2008 for the adjunctive treatment of seizures associated with LGS in patients 4 years of age and older.[3] It has also been studied in the management of refractory partial seizures.[1,2] This issue of *Pediatric Pharmacotherapy* will provide an overview of rufinamide and describe the results of initial clinical trials with this agent as an add-on antiepileptic in children and adults.

Mechanism of Action

Rufinamide, 1-[2,6-difluorophenyl)methyl]-1H-1,2,3-triazole-4 carboxamide), is a triazole derivative structurally unrelated to any other current antiepileptic drug. While the exact mechanism of rufinamide is still unknown, it is thought to act through modulation of sodium channels resulting in membrane stabilization. Rufinamide administration slows recovery after a prolonged prepulse in cortical neurons and limits sustained repetitive firing of sodium-dependent action potentials.[1-4]

Pharmacokinetics

Over a dozen studies have been conducted to define the pharmacokinetic profile of rufinamide in children and adults.[5] Clinical trials in adults receiving rufinamide have demonstrated a slow, but complete, absorption with a bioavailability approaching 85%. Peak plasma concentrations occur 3 to 6 hours after an oral dose. Food increases the extent of absorption by approximately 30 to 45% and shortens the time to maximum concentrations. Rufinamide is distributed evenly between erythrocytes and plasma with minimal protein binding (34%). The apparent volume of distribution in adults receiving 3,200 mg rufinamide/day was 50 L. Rufinamide is extensively metabolized via carboxylesterase-mediated hydrolysis to inactive compounds. Only 2% of a dose is excreted from the body as unchanged drug. The average elimination half-life of rufinamide in adults is 6 to 12 hours.[1,3-6]

The pharmacokinetic profile of rufinamide in children has been evaluated by the manufacturer in several trials.[2-7] The largest trial enrolled a total of 216 pediatric patients, 117 children between 4 and 11 years of age and 99 adolescents between 12 and 17 years of age. While the full results of this study have not yet been published, the data were reported as being similar to the values obtained in adults.[4] Making a comparison to adult studies is complicated, however, by differences in concomitant medications. The pediatric patients in clinical trials are often being treated with valproic acid, which increases rufinamide concentrations, while most adult patients are treated with antiepileptics that decrease rufinamide concentrations.[5]

Clinical Trials

A number of studies were conducted with rufinamide prior to its approval by the FDA. The largest was a multicenter, randomized, double-blind, placebo-controlled add-on trial in patients with refractory simple or complex partial seizures. A total of 647 patients, ages 15 to 65 years, were enrolled. The primary aim of the study was to evaluate efficacy and safety over the proposed dosage range of 200 to 1,600 mg/day.

After a 3-month baseline observation phase, patients were randomized to one of four rufinamide dosages (200, 400, 800, or 1,600 mg/day divided into two daily doses) or placebo.[1,2]

Efficacy was assessed by the seizure frequency ratio (the difference between the number of seizures at baseline and during treatment). The ratio was +5% in the placebo group, compared to 0% in the 200 mg/day group, -7% in the 400 mg/day group ($p<0.03$), -11% in the 800 mg/day group ($p<0.02$), and -12% in the 1,600 mg/day group ($p<0.02$). The percentage of patients with a 50% or greater reduction in seizure frequency at 28 days was 5% in the placebo group, 4.7% in the 200 mg/day group, 16% in the 400 mg/day group, 11.6% in the 800 mg/day group, and 14.3% in the 1,600 mg/day group.[1,2] The results of this study formed the basis of the FDA approval.

In 2001, Palhagen and colleagues published the results of another multicenter, randomized, double-blind, placebo-controlled add-on trial of rufinamide in adults with partial or primary generalized tonic-clonic seizures.[8] Fifty patients were randomized to receive either rufinamide, beginning at 400 mg/day and increased at weekly intervals to 1,600 mg/day, or placebo for 28 days. At the end of the trial, seizure frequency had decreased by 41% in the rufinamide group, while it had increased by 52% in the placebo group. A 50% or greater reduction in seizure frequency from baseline was achieved in significantly more of the rufinamide patients (39%) than controls (16%, $p=0.096$). The most frequently reported adverse effects in the rufinamide group were fatigue (20%), headache (12%), and tremor (12%). These results added further evidence that rufinamide is a safe and effective adjunct therapy for patients with refractory epilepsy.

Two additional rufinamide studies were published last year.[9,10] Glauser and colleagues conducted a randomized double-blind, placebo-controlled add-on trial of rufinamide in 138 patients with LGS.[9] The patients ranged from 4 to 30 years of age. All had a minimum of 90 seizures per month at the time of enrollment and evidence of a slow spike and wave pattern on electroencephalogram (EEG). After a 28-day baseline observation period, patients were randomized to receive rufinamide or placebo for 84 days. Dose titration was conducted over the first two weeks, followed by a 70-day maintenance phase. Rufinamide was initiated at a dose of 10 mg/kg/day and titrated by 10 mg/kg/day increments every two days to a maximum of 45 mg/kg/day or 3,200 mg/day.

The median reduction in seizure frequency was 32.7% in the rufinamide group versus 11.7% ($p=0.0015$). The frequency of drop attacks decreased by 42.5% in the rufinamide group, but increased in the placebo group by 1.4% ($p<0.0001$). The rufinamide group also had significantly more patients who experienced a 50% or greater reduction in seizure frequency (31.1% versus 10.9%, $p=0.0045$). There was no difference in the number of patients who achieved complete seizure control (4.1% in the rufinamide group versus 3.3% of controls, $p=0.84$). There was also no significant difference between the groups in the parent/guardian global evaluation (median score 2.30 for rufinamide and 1.77 for placebo). The primary adverse effects reported with rufinamide included somnolence (24.3%) and vomiting (21.6%). Based on their results, the authors concluded that rufinamide was an effective and relatively well-tolerated adjunctive therapy in patients with LGS.[9]

Kluger and colleagues recently published the results of an observational study of rufinamide as an add-on therapy in children and adults with refractory epilepsy.[10] The study incorporated data from institutions throughout Germany and Austria. A total of 60 patients were evaluated, including 45 children and 15 adults (mean patient age 14.5 ± 11.6 years, range 1-50 years). The indications for treatment were as follows: LGS (31 patients), idiopathic generalized epilepsy syndromes (5), cryptogenic unclassified generalized seizures (7), and partial epilepsy (17). The average number of antiepileptics used in the study patients prior to enrollment was 11 ± 4 (range 4 to 20). The most frequent concomitant therapies during the study were valproic acid, used in 43.3% of the patients, and clobazam, used in 28.3%. Nine patients were on a ketogenic diet, 14 patients had a vagus nerve stimulator, and eight patients had undergone unsuccessful epilepsy surgery.

While the choice of rufinamide dose was determined by the treating physician, the most common initial rufinamide dose used in the study patients was 10 mg/kg/day. The mean final dose was 35.5 ± 17.3 mg/kg/day. Efficacy was evaluated by comparing baseline seizure frequency with results after at least 4 weeks of treatment and again at 12 weeks. A 50% or greater reduction in seizure frequency occurred in 46.7% of the treated patients. Twenty percent achieved a 75% or greater reduction in seizures and 8.3% achieved complete seizure control.

The highest response rate was achieved in the patients with LGS (54.8%). Patients with refractory partial seizures were the least likely to respond to rufinamide (23.5%). The most frequently reported adverse effects were fatigue (18.3%), vomiting (13.3%), and loss of appetite (10%). No serious adverse effects were observed by the investigators. This preliminary observational study confirms the results with rufinamide demonstrated in clinical trials and supports its use as an adjunctive antiepileptic therapy.[10]

Warnings and Precautions

Rufinamide is contraindicated in patients with known or suspected short QT syndrome. In clinical trials, rufinamide shortened the QT interval up to 20 msec or greater. There were no cases of QT intervals < 300 msec or reports of drug-induced ventricular arrhythmias or sudden cardiac death. Patients taking other drugs that might shorten the QT interval should not take rufinamide.[3,4]

Rufinamide also carries the black box warning for suicidal ideation common to all antiepileptic drugs. Although there are not adequate data to determine if rufinamide use places patients at higher risk for suicide, patients and their families should be aware of this risk and the need to discuss changes in mood or behavior with their physician.[3,4]

Rufinamide has also been associated with antiepileptic multi-organ system hypersensitivity reactions. The initial presentation in clinical trials with rufinamide has been fever and rash. Patients typically progress to development of hematuria, lymphadenopathy, and elevated serum transaminases. In the cases reported during premarketing clinical studies, symptoms resolved after discontinuation of therapy.[3,4]

Adverse Effects

In premarketing clinical trials in children, rufinamide has generally been well-tolerated. The most frequently reported adverse effects have been central nervous system-related: somnolence (in 17% of patients based on combined study results), headache (16%), fatigue (9%), dizziness (8%), ataxia (4%), and psychomotor hyperactivity, aggression, or inattention (3%). Other adverse effects included vomiting (17%), nausea (7%), loss of appetite, nasopharyngitis, influenza (5%), rash, diplopia (4%), and abdominal pain, pruritus, bronchitis, sinusitis, and ear infections (3%). Similar reactions were reported in studies conducted in adults. In combined data from pediatric and adult rufinamide trials, approximately 4% of patients developed leukopenia (WBC < $3x10^9$L).[1-4]

The average rate of discontinuation of therapy in pediatric trials was 8 to 9%, similar to rates in clinical trials conducted in adults. The most frequent reasons for discontinuation were continued seizures, rash, or fatigue (each reported in 2% of patients), or vomiting (1%).[1-4]

Drug Interactions

Rufinamide is weak inducer of cytochrome P450 (CYP) 3A4. Concomitant administration of rufinamide and triazolam or oral contraceptives may reduce the concentrations of these drugs. Triazolam area under the concentration curve (AUC) values may be decreased by up to 30-40%. Ethinyl estradiol and norethindrone AUC values have been reduced by 22% and 14%, respectively, in clinical studies. While the impact of this reduction on oral contraceptive efficacy is not known, it is recommended that women of child-bearing age use an additional form of contraception during treatment. Rufinamide is also a weak inhibitor of CYP2E1, but no drug interactions resulting from this effect have been identified.[1-4]

Concomitant administration of rufinamide and other antiepileptic drugs has been studied in both children and adults. In general, children, especially those receiving higher rufinamide doses, appear to have the most significant drug interactions. Rufinamide has no significant effect on the concentrations of topiramate or valproate. It may decrease concentrations of carbamazepine or lamotrigine by 7 to 13%. In contrast, rufinamide may increase serum concentrations of phenobarbital and phenytoin by 7 to 21%.[1-4]

Several antiepileptic drugs alter rufinamide concentrations. Administration of phenobarbital, primidone, or phenytoin may decrease rufinamide concentrations by up to 25 to 46%. Carbamazepine may decrease rufinamide concentrations by 19 to 26%. Vigabatrin decreases rufinamide concentrations by approximately 13%. Concomitant administration of valproic acid derivatives may increase rufinamide concentrations by 16 to 70%. The magnitude of the effect depends on the serum valproate concentration. Pediatric patients receiving rufinamide should have a slow introduction of the valproic acid/valproate product with gradual dose titration. Benzodiazepines, lamotrigine, and topiramate have no significant effect on rufinamide concentrations.[1-5]

Dosing Recommendations and Availability

The recommended starting dose for rufinamide in children is 10 mg/kg/day divided into two doses per day. The dose may be increased by 10 mg/kg increments every 2 days up to a dose of 45 mg/kg/day or 3,200 mg/day. For adults, the recommended starting dose is 400 to 800 mg/day divided into two doses per day. The dose may be increased by 400 to 800 mg/day increments every 2 days until a maximum dose of 3,200 mg/day is reached. No dosage adjustment is needed in patients with renal dysfunction. Hemodialysis may reduce serum concentrations by approximately 30%. Dosage adjustment may be necessary based on clinical response. Use of rufinamide is not recommended in patients with hepatic impairment.[1-4]

Rufinamide (Banzel®; Eisai Co., Ltd.) is available as 200 mg and 400 mg scored tablets. The tablets may be crushed, if necessary, for patients unable to swallow them whole. Rufinamide should be taken with food to improve absorption. If therapy is going to be discontinued, the dose should be gradually reduced to minimize the risk of precipitating seizures. In clinical trials, the dose was reduced by 25% every two days.[3,4]

Cost

The average wholesale price (AWP) for a bottle of 30 200 mg rufinamide tablets is $46.88. The AWP for a bottle of 120 400 mg tablets is $375.00, resulting in an approximate daily cost of therapy of $3.00 to $6.00.[11]

Summary

Rufinamide is a useful new option for the adjunctive treatment of patients with LGS or refractory partial seizures. While initial clinical trials have demonstrated benefit and an acceptable safety profile, further studies are needed to define further the place of rufinamide in therapy and to identify rare or serious adverse effects.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/27/09:

1. Clevidipine butyrate (Cleviprex®), and IV calcium channel blocker, was added to the Inpatient Formulary with restriction to use in perioperative blood pressure management in patients undergoing cardiac or vascular surgery.
2. Fosfomycin (Monurol®), a broad-spectrum antibiotic, was added to the Inpatient Formulary for the treatment of uncomplicated urinary tract infections in women. It is a Category A antimicrobial.
3. Oral doxercalciferol (Hectorol®), a synthetic vitamin D analog, was added to the Inpatient and Outpatient Formularies for the treatment of secondary hyperparathyroidism associated with chronic kidney disease.
4. A second oral live rotavirus vaccine (Rotarix®) was added to the Formulary. Unlike RotaTeq®, this vaccine requires only two doses for full immunization. RotaTeq® will be removed after the patients who have already started immunization with it have completed the series.
5. The restriction on caspofungin was amended to require approval by a Pediatric ID attending physician. The approving physician's name will be added to the medical order by the prescriber.

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