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Original Articles

Experience With Rufinamide in a Pediatric Population: A Single Center's Experience

Martina Vendrame, MD, PhD*[1], Tobias Loddenkemper, MD*†[1], Vasu D. Gooty, MD*†, Masanori Takeoka, MD*†, Alexander Rotenberg, MD, PhD*†, Ann M. Bergin, MD*†, Yaman Z. Eksioglu, MD*†, Annapurna Poduri, MD*†, Frank H. Duffy, MD*†, Mark Libenson, MD*†, Blaise F. Bourgeois, MD*†, and Sanjeev V. Kothare, MD*†

Rufinamide is a new antiepileptic drug recently approved as adjunctive treatment for generalized seizures in Lennox-Gastaut syndrome. We undertook a retrospective analysis of 77 patients with refractory epilepsy and receiving rufinamide to evaluate the drug's efficacy, tolerability, safety, and dosing schedules. It appeared efficacious in diverse epilepsy syndromes, with the highest responder rate in focal cryptogenic epilepsies (81.1% of patients with >50% response rate), and in diverse seizure types, with the highest responder rate in tonic/atonic and partial seizures (48.6% and 46.7% of patients with >50% response rate, respectively). Rufinamide was well tolerated: only 13% of patients developed side effects necessitating drug withdrawal. These findings suggest that rufinamide may possess good efficacy and tolerability, and that its efficacy may extend to epilepsy syndromes beyond Lennox-Gastaut, including both partial and generalized epilepsy syndromes.

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Introduction

Rufinamide is a novel antiepileptic drug recently reported to possess a favorable pharmacokinetic profile, with rapid and almost complete oral absorption, low plasma protein-binding, high renal excretion, and low propensity to drug-drug interactions [1,2]. Although these properties make rufinamide a potentially useful drug in the treatment of intractable epilepsy in children, rufinamide is currently only approved for the adjunctive treatment of generalized seizures in Lennox-Gastaut syndrome.

In this study, we retrospectively analyzed the use of rufinamide in children with diverse epilepsy syndromes in a tertiary pediatric epilepsy center. We describe the safety, tolerability, efficacy, and dosing of rufinamide, to identify the advantages or difficulties of its use across a diverse spectrum of seizure types and epilepsy syndromes. This report is the first American post-marketing survey of rufinamide in children since its approval by the United States Food and Drug Administration in November 2008.

Patients and Methods

This study was approved by the Institutional Review Board of Children's Hospital Boston (Boston, MA). We identified patients who had commenced treatment with rufinamide between January 1 and November 1, 2009, in the Division of Epilepsy and Clinical Neurophysiology at Children's Hospital Boston. We collected data retrospectively regarding age, sex, seizure types, epilepsy syndromes, underlying cause of seizures (when known), rufinamide dosing and titration schedule, concurrent antiepileptic drug therapy, duration of follow-up, side effects, and rates of discontinuation. Efficacy was based on seizure frequency 3 months before the initiation of rufinamide treatment, and on rufinamide therapy up to the follow-up visit. Data were obtained from a seizure count by the patient's caretaker. Changes in seizure frequency and 50% responder rate (i.e., the percentage of patients with >50% seizure reduction) according to syndrome or seizure type were analyzed. Tolerability and safety were assessed by evaluating side effects and adverse events reported by the children and

From the *Department of Neurology, Harvard Medical School, Boston, Massachusetts; and †Division of Epilepsy and Clinical Neurophysiology, Children's Hospital Boston, Boston, Massachusetts.
[1] Both authors contributed equally to this work.

Communications should be addressed to:
Dr. Kothare; Division of Epilepsy and Clinical Neurophysiology; Children's Hospital Boston; 300 Longwood Avenue, Fegan 9; Boston, MA 02115.
E-mail: Sanjeev.kothare@childrens.harvard.edu
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their caretakers to the treating epileptologist. There were no exclusion criteria.

Seizure types and epilepsy syndromes were classified according to the International League Against Epilepsy [3,4]. A statistical analysis of nonparametric measures was conducted using SPSS software, version 11.0, for Macintosh Computers (SPSS, Inc., Chicago, IL).

Results

Ninety-one patients were prescribed rufinamide during the 10-month study period. Of those 91 patients, 77 actually commenced use of the drug, and represent the study subjects. Fourteen patients had been prescribed but had not commenced using rufinamide by the time of initiating the study. The demographic and clinical characteristics of patients receiving rufinamide are reported in Table 1. The median patient age was 12 years (range, 1-27 years). The median duration of follow-up was 4.4 months (range, 1-10 months).

The median starting dose was 8.8 mg/kg/day (range, 1-41 mg/kg/day), and the median maintenance dose was 33.8 mg/kg/day (range, 5-100 mg/kg/day). The median time to reach the maximum dose was 83.7 days (range, 10-180 days). All 77 patients were receiving concurrent antiepileptic drug therapy at the time of their most recent clinic follow-up. This therapy consisted of one agent (11 patients), two agents (29 patients), three agents (26 patients), or more than three agents (11 patients). The most commonly used antiepileptic drugs in addition to rufinamide included levetiracetam, lamotrigine, sodium valproate, benzodiazepines, and zonisamide. Concurrent medications were continued at a stable dose during rufinamide therapy. The responder rate, as defined by a reduction in seizure frequency of 50% or more, was 51% (39/77 patients).

Of 77 children, 10 (13%) experienced only one seizure type, 34 (44%) experienced two seizure types, and 32 (42%) experienced three or more seizure types. The median percentage of seizure reduction and the responder rate for each seizure type after the introduction of rufinamide are presented in Table 2. Responder rates were highest among children with tonic/atonic and partial seizures. The median percentage of seizure reduction and the response rate for each epilepsy syndrome after the introduction of rufinamide are presented in Table 3. Focal cryptogenic seizures yielded the best responder rates, whereas West syndrome yielded the lowest responder rate. Early response was also evident at doses as low as 10 mg/kg/day, with no further benefits above the recommended dose. Similarly, no correlation was evident between decrease in seizure frequency and number or type of antiepileptic drugs used together with rufinamide.

Side effects were reported by 23 (29%) of 77 patients, and included drowsiness in 10 (13%), rash in five (6%), dizziness in four (5%), nausea and vomiting in three (3%), anorexia in two (2%), headache in one (1%), and visual disturbance in one (1%). Most of these side effects were transient. Side effects appeared to occur earlier during the escalation, with the onset of most side effects experienced at doses as low as 4 mg/kg/day. Two patients tolerated doses as high as 100 mg/kg/day without side

Table 1. Demographic and clinical characteristics of 77 patients receiving rufinamide

Characteristics	Number of Patients (%)
Sex	
Male	41 (53)
Female	36 (47)
Epilepsy syndrome	
Lennox-Gastaut syndrome	26 (33)
West syndrome	7 (9)
Focal cryptogenic seizures	12 (14)
Focal symptomatic seizures	32 (42)
Seizure types	
Generalized tonic-clonic	48 (62)
Tonic/atonic	37 (48)
Partial seizures	30 (38)
Infantile spasms	13 (16)
Myoclonic seizures	13 (16)
Absence	12 (15)
Etiology (if known)	
Malformation of cortical development	22 (28)
Cerebrovascular accident	11 (14)
Other	6 (7)
Concomitant antiepileptic drugs	
Levetiracetam	33 (42)
Lamotrigine	29 (37)
Benzodiazepines	27 (35)
Valproate	26 (33)
Zonisamide	24 (31)
Topiramate	17 (22)
Carbamazepine	6 (7)
Phenobarbital	4 (5)
Phenytoin	2 (2)

Table 2. Response of seizure types to rufinamide

Seizure Type (Number of Patients)	Median Percentage of Seizure Reduction	Percentage of Patients With a >50% Response (Number of Patients)
Generalized tonic-clonic (48)	33.33%	37.5% (18)
Tonic/atonic (37)	58.33%	48.6% (18)
Partial seizures (30)	50%	46.7% (14)
Infantile spasms (13)	37.5%	30.8% (4)

Table 3. Response of epilepsy syndromes to rufinamide

Seizure Type (Number of Patients)	Median Percentage of Seizure Reduction	Percentage of Patients With a >50% Response (Number of Patients)
Lennox-Gastaut syndrome (26)	50%	38.4% (10)
West syndrome (7)	25%	14.3% (1)
Focal cryptogenic seizures (12)	77.7%	83.3% (10)
Focal symptomatic seizures (32)	74.2%	31.3% (10)

Table 4. Review of premarketing clinical studies of rufinamide

Reference	Number of Patients	Age Range	Number of Pediatric Patients	Interventions	Criteria for Patient Selection	Key Outcomes of RUF vs Placebo
Palhagen et al., 2001 [5]	n = 50 (25 receiving RUF, and 25 receiving placebo)	18-60 yr	NA	Placebo or RUF for 28 days.	Partial seizures or primary GTCS, on four baseline AEDs at fixed dosage. Patients maintained constant plasma levels for at least 4 weeks before initiation of RUF.	Median change in seizure frequency: 41% decrease vs 52% increase ($P = 0.04$). Response rate for seizure frequency: 39% vs 16% ($P = 0.096$).
Glauser et al., 2005 [12]	n = 268	4-16 yr	n = 268	Placebo or RUF for 28 days. RUF titrated to 45 mg/kg/day in 14 days, followed by 77 days of maintenance.	Uncontrolled partial seizures; taking 1-2 AEDs at fixed doses.	Median change seizure frequency: 11.7% vs 14.0% ($P = 0.082$). Response rate for seizure frequency: 27.2% vs 18.3% ($P = 0.06$).
Biton et al., 2005 [6]	n = 153 (78 receiving RUF, and 75 receiving placebo)	4-63 yr	NA	Placebo or RUF for 28 days.	Uncontrolled primary GTCS on 1-2 AEDs at fixed doses, with at least three GTCS during baseline phase, and at least one seizure during 28-day baseline period.	Median change in seizure frequency: 36.4% vs 25.6% ($P = 0.63$)
Glauser et al., 2008 [7]	n = 138 (74 receiving RUF, and 64 receiving placebo)	4-37 yr	n = 40, aged 4-17 yr	Placebo or RUF target dose of 45 mg/kg/day for 84 days.	Patients with LGS, with at least 90 seizures per month before 28-day baseline period, on 1-3 AEDs as baseline medications; absence of progressive brain injury.	Median change in total seizure frequency: 32.7% decrease vs 11.7% decrease ($P = 0.0015$). Median change in tonic-atonic seizure frequency: 42.5% decrease vs 1.4% increase ($P < 0.0001$). Response rate for total seizure frequency: 31.1% vs 10.9% ($P = 0.0045$). Response rate for tonic/atonic seizures: 42.5% vs 16.7% ($P = 0.002$).
Brodie et al., 2009 [9]	n = 313 (156 receiving RUF, and 157 receiving placebo)	16-72 yr	NA	Placebo or RUF for 56 days.	Partial seizures, and receiving 1-2 AEDs on fixed dose during 8-week baseline period; absence of progressive brain injury.	Median change in seizure frequency: 20.4% decrease vs 1.6% increase ($P = 0.02$). Response rate for seizure frequency: 28.2% vs 18.6% ($P = 0.04$).

Abbreviations:
AEDs = Antiepileptic drugs
GTCS = Generalized tonic-clonic seizures
LGS = Lennox-Gastaut syndrome
NA = Not available
RUF = Rufinamide

effects. The presence of side effects did not depend on the number or type of antiepileptic drug co-medications. The discontinuation rate was 13% (n = 10), attributable to intolerability in all cases, as well as lack of efficacy in four patients (5%) or worsening seizures in three patients (3%). Side effects that led to the discontinuation of rufinamide included drowsiness (five patients), rash (three patients), headache (one patient), and loss of vision (one patient). Rufinamide levels were not available for any patient.

Discussion

This retrospective study suggests that rufinamide may be a useful adjunctive treatment in children with refractory epilepsy. It was efficacious in diverse epilepsy syndromes, with a maximal responder rate in focal cryptogenic seizures, and in diverse seizure types, with a maximal responder rate in tonic/atonic and partial seizures.

To date, a limited number of randomized clinical trials and open label studies have described the use of rufinamide

in the pediatric population. Published premarketing studies on rufinamide are listed in Table 4. To the best of our knowledge, no post-marketing American studies on rufinamide have been undertaken. The recent open data reported by Kluger et al. [8] on 45 pediatric patients indicated a response rate of 46.7%, which is similar to the response in the present study (50%). However, that same study reported a low response rate for partial epilepsy (23%, 4 /17) relative to Lennox-Gastaut syndrome (54.5%, 17/31) and unclassified generalized epilepsies (42.8%, 3/7).

In the present study, rufinamide was well tolerated, even at doses up to 100 mg/kg/day, with 29% experiencing side effects but only 13% in need of drug withdrawal. Others reported a similar side effect profile, but with a higher incidence [8]. Although the present study does not allow us to draw meaningful conclusions about dose or titration schedules, a slower titration with 10 mg/kg weekly increments was used in many of our patients, i.e., a much slower titration than what is recommended in the packet insert. We must also take into account the present study's lack of fixed titration schedules. Therefore, the effect of schedule modifications based on observed side effects is likely reflected in the lack of correlation between different titration rates, side effect profiles, and subsequently lower titration rates. From the perspective of patients' safety, we would recommend slower titration, in an attempt to decrease the incidence of side effects and to avoid discontinuation of the drug.

Data on possible rufinamide-drug interactions were not collected in the present study. Although the mean plasma rufinamide concentration to reduce seizure frequency by 25-50% is predicted to be 15-30 μg/mL [1], at the time of our analysis, rufinamide blood levels were not available. Certain medications such as cytochrome P450 enzyme inducers, e.g., phenobarbital, primidone, phenytoin, and carbamazepine, can increase the clearance of rufinamide [9]. The coadministration of these antiepileptic drugs with rufinamide can lead to significantly decreased rufinamide levels and decreased efficacy, and therefore these patients may need higher doses of rufinamide [9,10]. On the other hand, valproate administration may cause an elevation of rufinamide concentrations [10]. This effect appears to be more dramatic in children, with a 60-70% increase in rufinamide levels [1,11].

Because of the retrospective nature of our study, the assessment of seizure frequency may involve considerable methodological difficulties. This observational study did not include a control group. Because of its relatively small numbers, we could not assess which antiepileptic drugs were most efficacious when used in combination with rufinamide. The study approach led to variable intervals between pre- and post medication initiation assessment. There were no inclusion/exclusion criteria nor standardized protocols for medication administration. Selection bias attributable to the acquisition of data at a tertiary epilepsy center, along with referral bias, also constituted a limiting factor.

Taken together, our observations suggest that rufinamide may be a useful adjunctive antiepileptic drug not only for generalized seizures in Lennox-Gastaut syndrome, but also for a wide range of other seizure types and epilepsy syndromes. In particular, we report promising evidence in the treatment of focal cryptogenic epilepsies and partial seizures.

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