Original article

Epileptic Disord 2013; 15 (1): 49-54

Short-term efficacy and tolerability of rufinamide adjunctive therapy in children with refractory generalised epilepsy

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Received March 29, 2012; Accepted January 09, 2013

ABSTRACT – We evaluated the efficacy and tolerability of rufinamide adjunctive therapy in children with refractory generalised epilepsy. The study cohort consisted of 20 patients with Lennox-Gastaut syndrome, 5 with Dravet syndrome, and 28 with unclassified refractory generalised epilepsy. Patients with more than 50% seizure reduction at three and six months were defined as responders. The overall response rate was 37.7% at three months and 34.0% at six months. At three months, patients with Lennox-Gastaut syndrome (40.0%) and epilepsy with spasms/tonic seizures (38.5%) showed higher response rates than those with Dravet syndrome (20.0%) and epilepsy with myoclonic seizures (20.0%). High response rates in patients with Lennox-Gastaut syndrome (30.0%) and epilepsy with spasms/tonic seizures (38.5%) were sustained throughout the six-month study. The accuracy of, and differences between, responder rates should, however, be interpreted with caution due to the small number of patients. Overall, rufinamide appeared to be effective and reasonably well tolerated in this group of children with refractory generalised epilepsies, although a subgroup of patients with Dravet syndrome and epilepsy with myoclonic seizures were less responsive to rufinamide treatment.

Key words: rufinamide, generalized epilepsy, anticonvulsant, children

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doi:10.1684/epd.2013.0557

Rufinamide, a triazole derivative (1-[2,6-difluorophenyl]methyl)-1-hydro-1,2,3-triazole-carboxamide), is a novel antiepileptic drug which has a different chemical structure from other antiepileptic drugs. Favourable characteristics as an antiepileptic drug include a broad spectrum of anticonvulsant activity, good oral absorption, low propensity for drug interactions, and a modest side effect profile (Cheng-Hakimian *et al.*, 2006). Studies have demonstrated its efficacy in various

animal models of partial, generalised tonic-clonic, absence, and clonic seizures (Hakimian *et al.*, 2007). Premarketing studies have suggested that rufinamide is efficacious in the treatment for both partial and generalised seizures (Pålhagen *et al.*, 2001). However, currently, the drug is approved only for use as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome.

Studies of rufinamide treatment in heterogeneous groups, mainly focusing on Lennox-Gastaut syndrome (Coppola *et al.*, 2010; Vendrame *et al.*, 2010), have shown promising results (Kluger *et al.*, 2009; Kluger *et al.*, 2010a; Coppola *et al.*, 2011). Additionally, some recent studies conducted for one or two specific epilepsy syndromes, such as epileptic spasms (Olson *et al.*, 2011) and epilepsy with myoclonic absences (Häusler *et al.*, 2011), have demonstrated that rufinamide is effective in the treatment for other epilepsy syndromes as well. In contrast to the favourable responses for other generalised epilepsies, a recent study reported a disappointing outcome of rufinamide treatment in patients with Dravet syndrome (Mueller *et al.*, 2011).

Inhibition of sodium channel activity has generally been postulated to be the principal mechanism of rufinamide action (Arroyo, 2007). However, since other drugs that act at the sodium channel, such as carbamazepine and phenytoin, are known to aggravate myoclonic and atypical absence seizures (Somerville, 2009), rufinamide may also elicit similar responses. Thus, the responses in patients with specific seizure types or syndromes should be further delineated in order to determine the efficacy of rufinamide in the context of each disorder and establish the most favourable indications for this drug.

In this study, we evaluated the efficacy and safety of rufinamide adjunctive therapy in children with refractory generalised epilepsy, and further assessed the efficacy of rufinamide in related epilepsy syndromes and seizure types.

Methods

A retrospective chart review was performed with the approval of the Institutional Review Board of Seoul National University Children's Hospital. Sixty-five children with epilepsy received rufinamide in the Pediatric Neurology Division of the above-mentioned hospital from May 2010 to April 2011. Data from the charts of 53 children meeting the following criteria were analysed: (1) between 4 and 18 years of age; (2) diagnosed with generalised epilepsy by EEG or video-EEG; (3) more than one seizure per month; and (4) seizures refractory to at least two antiepileptic drugs. Twelve children were excluded because they received either a ketogenic diet or had a corpus callosotomy during the study period. Patients with only absence seizures were not included since absence seizures are often difficult to define and count.

Baseline data was obtained from the medical records of each patient. Age, sex, underlying aetiology, body weight, previous seizure types and diagnosis, presence of mental retardation/developmental delay, concomitant drug use, magnetic resonance images, video-EEG records, and EEG results were collected and reviewed. Seizure semiology, seizure frequency, rufinamide start and end dates, initial dose, maximal dose, and adverse events reported during the study period were assessed.

The diagnosis of each patient was established based on the International League Against Epilepsy (1981, 2010) classification of seizures and epilepsy syndromes. Patients were classified as having Lennox-Gastaut syndrome only when they had tonic seizures documented on medical records or based on video-EEG, intractable seizures, mental retardation, and slow spike-wave discharges on EEG. Patients were classified as having Dravet syndrome when they had had normal development before seizure onset, seizures starting before 1 year of age, seizures mainly triggered by fever, prolonged convulsive seizures (longer than 15 minutes), later occurrence of seizures of various types, and later cognitive regression (Depienne *et al.*, 2009). Diagnoses were supported by genetic analysis, if possible. If patients could not be diagnosed with any specific epilepsy syndrome, they were further classified as having epilepsy with spasms/tonic seizures or epilepsy with myoclonic seizures according to their predominant seizure types. Seizures were classified according to the International League Against Epilepsy classification and were identified based on either previous video-EEG monitoring or current clinical examinations. Absences or partial seizures reported by caregivers were classified as "others".

Baseline seizure frequency was determined by asking caregivers to count different seizure types separately during the month before the initiation of rufinamide. Then, the frequency of each seizure type was evaluated during each visit to the clinic by asking the caregivers to estimate the frequency of seizures during the follow-up period, relative to the baseline. The efficacy of treatment was determined by assessing the total monthly seizure frequency and individual seizure types at three months and six months after rufinamide initiation. Patients were classified into the following four categories, according to the percentage of seizure reduction: (1) seizure-free; (2) seizure reduction $\geq$50%; (3) seizure reduction $<$50%; and (4) no change or aggravation of seizures. Patients with more than 50% seizure reduction were defined as responders.

The initial dose of rufinamide ranged from 5-20 mg/kg/day. Each patient then visited the clinic regularly every 2-4 weeks, and the dose of rufinamide was increased by 10-20 mg/kg at each visit, depending on the response. The maximum dose for each patient varied from 20-80 mg/kg/day. Adverse events reported by patients or caregivers during rufinamide therapy were recorded.

Results

Patient characteristics

Of the 53 enrolled subjects, 20 had Lennox-Gastaut syndrome. The rest of the patients included 5 with Dravet syndrome and 28 with unclassified generalised epilepsy. Among patients with unclassified generalised epilepsy, 13 were further classified as having epilepsy with spasms/tonic seizures and 5 were further classified as having epilepsy with myoclonic seizures.

The mean follow-up period was 9.9 months (range: 6-12 months) and the mean duration of rufinamide treatment was 7.6 months (range: 0.4-12 months). The mean initial dose was 12.4 mg/kg/day (range: 5.6-23.5 mg/kg/day), and the mean maximal dose was 40.2 mg/kg/day (range: 6.7-83.3 mg/kg/day). Additional patient characteristics are listed in *table 1*.

The mean number of concomitant antiepileptic drugs was 3.6 (range: 1-6). Four patients with Lennox-Gastaut syndrome had more than five baseline antiepileptic drugs, and these patients had multiple seizure types that were very sensitive to changes in antiepileptic drugs. The most frequently used antiepileptic drugs at the time of rufinamide treatment were lamotrigine (37/53), levetiracetam (28/53), topiramate (28/53), clobazam (26/53), and valproate (18/53). A comparison of response rates in patients receiving different concomitant antiepileptic drugs showed no statistically significant difference (data not shown).

Table 1. Patient characteristics.

Characteristics	Value
Male : Female	32:21
Mean age (years)*	7.9 (4-17.3)
Symptomatic	22
Hypoxic-ischemic encephalopathy	11
Malformation of cortical development	4
Neurocutaneous syndrome	2
Others	5
Cryptogenic	31
Epilepsy syndrome	
Lennox-Gas taut syndrome	20
Dravet syndrome	5
Unclassified generalized epilepsy	28
Epilepsy with spasms/tonic seizures	13
Epilepsy with myoclonic seizures	5
History of ketogenic diet	22
History of corpus callosotomy	6
Number of concomitant antiepileptic drugs*	3 (1-6)

* Median, range

Efficacy

Among the 53 patients, 37.7% (20/53) were classified as responders at three months. The number of responders decreased to 34.0% (18/53) at six months. The number of seizure-free patients was 9 (17.0%) and 5 (9.4%) at three and six months, respectively.

When outcomes were evaluated according to epilepsy syndromes, 40.0% (8/20) of patients with Lennox-Gastaut syndrome had more than 50% seizure reduction at three months. Twenty per cent (1/5) of patients with Dravet syndrome responded to rufinamide therapy. Patients with unclassified generalised epilepsy showed a response rate of 39.3% (11/28), and when these patients were further subdivided according to their predominant seizure types, those with epilepsy and spasms/tonic seizures showed a response rate of 38.5% (5/13), while those with epilepsy and myoclonic seizures had a response rate of 20.0% (1/5). This trend was sustained for six months. Detailed results are presented in *table 2*.

The response rates for each seizure type after three and six months of rufinamide therapy are presented in *table 3*. The response rates related to seizure type ranged from 21.1 to 60.0% at three months; tonic-clonic seizures (60.0%; 3/5), tonic seizures (32.3%; 10/31), atonic seizures (36.4%; 4/11), spasms (55.6%; 5/9), and myoclonic seizures (21.1%; 4/19).

When response rates for each seizure type were evaluated in patients with Lennox-Gastaut syndrome exclusively, response rates for atonic head drops, tonic seizures, and tonic-clonic seizures were 66.7% (4/6), 60% (9/15), and 33.3% (1/3), respectively. The response rates were lower for myoclonic seizures and spasms, at 16.7% (1/6) and 25.0% (1/4), respectively, in this patient group.

Safety and tolerability

Twenty-three (43.4%) patients or their carers reported 24 adverse events during the study. Somnolence, poor appetite, and behavioural changes were the most common problems. Other adverse events are described in *table 4*. Most of the adverse events were transient and mild. Adverse events all subsided spontaneously or after discontinuation of rufinamide. No specific concomitant anticonvulsants were found to increase the risk of adverse events (data not shown).

Table 2. Response to rufinamide according to epilepsy syndrome.

Epilepsy syndrome	*N*	3 months		6 months	
		Seizure-free (%)	>50% seizure reduction (%)	Seizure-free (%)	>50% seizure reduction (%)
Lennox-Gastaut syndrome	20	4 (20.0)	8 (40.0)	1 (5.0)	6 (30.0)
Dravet syndrome	5	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)
Unclassified generalized epilepsy	28	5 (17.9)	11 (39.3)	4 (14.3)	11 (39.3)
Epilepsy with spasms/tonic seizures	13	3 (23.1)	5 (38.5)	3 (23.1)	5 (38.5)
Epilepsy with myoclonic seizures	5	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)
Total	53	9 (17.0)	20 (37.7)	5 (9.4)	18 (34.0)

Table 3. Response to rufinamide according to seizure type.

Seizure type		3 months		6 months	
	N	Seizure free (%)	> 50% seizure reduction (%)	Seizure free (%)	> 50% seizure reduction (%)
Tonic	31	5 (16.1)	10 (32.3)	3 (9.7)	9 (29.0)
Myoclonic	19	1 (5.3)	4 (21.1)	1 (5.3)	4 (21.1)
Atonic	11	2 (18.2)	4 (36.4)	1 (9.1)	3 (27.3)
Spasms	9	2 (22.2)	5 (55.6)	1 (11.1)	3 (33.3)
Tonic-clonic	5	1 (20.0)	3 (60.0)	1 (20.0)	3 (60.0)
Others*	15	4 (26.7)	9 (60.0)	2 (13.3)	8 (53.3)

* Others, including absences and partial seizures

Rufinamide was discontinued in 14 patients (26.4%) during the study period; in 6 patients (11.3%) because there was no improvement in seizure frequency, and in a further 6 (11.3%) following an increase in seizure frequency. The results are shown in *table 5*. Two patients discontinued rufinamide due to adverse events (2/53; 3.8%); the reasons for discontinuation were the presence of a rash and behavioural problems.

Discussion

Although rufinamide was originally approved only for the treatment of Lennox-Gastaut syndrome (Glauser *et al*., 2008), many studies have recently investigated the efficacy of rufinamide for the treatment of other generalised epilepsy syndromes. However, most of these studies were performed in limited populations of patients with only a single epilepsy syndrome (Olson *et al*., 2011; Häusler *et al*., 2011; Mueller *et al*., 2011; Joseph *et al*., 2011), and a comparison of the outcomes between different epilepsy syndromes was not possible (Coppola *et al*., 2011). Since generalised epilepsy syndromes other than Lennox-Gastaut syndrome constitute a significant proportion of intractable generalised epilepsies, and specific syndromic classification is not always feasible, responses to rufinamide treatment for Lennox-Gastaut syndrome, unclassified generalised epilepsy, and other generalised epilepsy syndromes should be evaluated in patients together, as a single cohort.

In the present study, the overall response rates at three months and six months after initiation of rufinamide treatment (37.7 and 34%, respectively) were favourable. However, response tended to vary according to the specific epilepsy syndrome. While patients with Lennox-Gastaut syndrome and epilepsy with spasms/tonic seizures responded favourably, with up to a 40% response rate at three months, patients with Dravet syndrome only showed a 20% response rate at three months. Notably, patients with epilepsy and myoclonic seizures also showed a lower response rate (20%), similar to patients with Dravet syndrome. Patients with unclassified generalised epilepsy showed a response rate of 39.3% at three and six months.

These findings correlate well with previous studies. An earlier study conducted in patients with unclassified generalised epilepsy reported a similar response

Table 4. Adverse events reported by caregivers during rufinamide adjunctive therapy.

Adverse events	*N*	Number of patients who discontinued rufinamide (%)
Somnolence	8	
Poor appetite	5	
Behavioral problems	3	1 (1.9)
Enuresis	2	
Tremor	2	
Ataxia	1	
Drooling	1	
Nausea	1	
Rash	1	1 (1.9)

rate (42.8%) after three months of rufinamide therapy (Kluger *et al*., 2009). In another study, patients with epileptic spasms also showed a high response rate (52.6%; 20/38) (Olson *et al*., 2011), while a different study in patients with Dravet syndrome demonstrated a response rate of 20.0% (4/20) at six months (Mueller *et al*., 2011).

When the efficacy of rufinamide for different seizure types in Lennox-Gastaut syndrome was evaluated, the results were consistent with earlier studies. Atonic head drops were the best responding seizure type in earlier studies, as well as in this study, with response rates ranging from 47.0-78.9% after various durations of treatment (Kluger *et al*., 2009; Kluger *et al*., 2010b; Coppola *et al*., 2010; Vendrame *et al*., 2010). Tonic seizures also showed a good response rate in the above studies, while tonic-clonic seizures (response rate: 11.6-37.5%) (Kluger *et al*., 2009; Coppola *et al*., 2010) and spasms (response rate: 30.8%) (Vendrame *et al*., 2010) showed lower response rates, similar to the present study.

Worsening of seizures after rufinamide use occurred in 6 patients in the present study. Of the different epilepsy syndromes, this was most frequently associated with Dravet syndrome and myoclonic seizures were the most commonly aggravated seizure type. The low efficacy of rufinamide for the treatment of myoclonic seizures may be the reason for the poor outcome of patients with this syndrome. However, sodium channel-blocking agents, such as lamotrigine and carbamazepine, have been postulated to aggravate seizures by decreasing the sodium current density in inhibitory interneurons in patients with pre-existing loss of function of $Na_v1.1$ (voltage-gated sodium channel), such as patients with Dravet syndrome (Liao *et al*., 2010). The worsening of seizures with rufinamide, which is thought to act on sodium channels, may be attributable to a similar mechanism. An earlier study reported aggravation of seizures in 30% (6/20) of Dravet syndrome patients, but the specific type of seizure that was aggravated was not identified (Mueller *et al*., 2011). Further studies are required.

The adverse effects appear to be mild and transient with spontaneous resolution, according to previous short- and long-term studies of rufinamide therapy. Commonly reported effects were fatigue, poor appetite, and behavioural problems (Kluger *et al*., 2009). The present study showed similar results.

Table 5. Patients who experienced aggravation of seizures after rufinamide therapy.

Case	Age	Sex	Epilepsy syndrome	Habitual seizure	Aggravated or newly developed seizure	Duration of rufinamide therapy (days)	Initial rufinamide dose (mg/kg/d)
1	8	M	Dravet syndrome	Tonic	Tonic, tonic-clonic	29	20
2	15	M	Dravet syndrome	Myoclonic, atonic	Myoclonic status epilepticus	13	14
3	4	F	Dravet syndrome	Myoclonic, tonic-clonic	Myoclonic, tonic-clonic	14	14
4	7	M	Lennox-Gastaut syndrome	Tonic	Myoclonic	43	18
5	12	F	Lennox-Gastaut syndrome	Myoclonic	Myoclonic	34	14
6	1-1	M	Unclassified generalized epilepsy	Atonic, tonic-clonic	Absence status epilepticus	23	13

Among our 53 patients, 12 (24.5%) discontinued rufinamide during the study period. One patient discontinued due to rash, which developed after two months of therapy and subsided within five days after discontinuation. A recent study of patients with Lennox-Gastaut syndrome reported a higher occurrence of rash (2.7%) with rufinamide, compared to placebo (Kluger *et al*., 2010b). The development of rash with rufinamide use has also been reported in other studies (Vendrame *et al*., 2010; Joseph *et al*., 2011). Further studies to evaluate the prevalence of rash with rufinamide treatment are required.

This study has several limitations, including the study size and retrospective study design. This was an open-label study and did not include a control group. Only selected patients with very refractory epilepsy were included, and some epilepsy syndromes, such as myoclonic-atonic epilepsy, were excluded. Further prospective studies are required to assess the efficacy of rufinamide in these syndromes. In addition, when patients were stratified into different epilepsy syndromes, patient number per each group was very small, and consequently statistically significant changes would not have been expected because the study was under-powered. The confidence limits are very wide and the results should thus be interpreted with caution.

However, the value of this study is in the confirmation of recent reports which demonstrate the efficacy and tolerability of rufinamide treatment for patients with refractory generalised epilepsies, other than Lennox-Gastaut syndrome. The efficacy of rufinamide should be further evaluated in specific syndromes and seizure types, particularly since our current study suggests that rufinamide might have a low efficacy against generalised epilepsy syndromes presenting with myoclonic seizures. □

Acknowledgements and disclosures.

This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120099).

Ethical approval was obtained by the Institutional Review Boards of Seoul National University Hospital.A part of this work was presented as a poster at the 29th International Epilepsy Congress in Rome.

None of the authors has any conflict of interest to disclose.

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