ELSEVIER

Oxcarbazepine in Children With Nocturnal Frontal-Lobe Epilepsy

G. Praveen Raju, MD, PhD*, Dean P. Sarco, MD*†, Annapurna Poduri, MD*†, James J. Riviello, MD*†, Ann Marie R. Bergin, MD*†, and Masanori Takeoka, MD*†

Nocturnal frontal-lobe epilepsy is characterized by paroxysmal arousals, motor seizures with dystonic or hyperkinetic features, and episodic nocturnal wanderings. Carbamazepine is effective for seizure control in some of these patients, but seizures may be refractory to multiple antiepileptic drugs. We report on eight children between ages 4-16 years with nocturnal frontal-lobe epilepsy who had a dramatic response to oxcarbazepine at standard recommended doses, some of whom were refractory to previous antiepileptic medications. Brain magnetic resonance imaging, routine electroencephalogram, and prolonged, continuous video-electroencephalogram telemetry were performed in all children. Nocturnal frontal-lobe epilepsy was diagnosed by demonstrating ictal electroencephalogram changes originating from the frontal lobes. The children were followed for response of seizures to oxcarbazepine, side effects, and routine blood tests, including serum 10-monohydroxide derivative levels. The mean oxcarbazepine dose was 30.4 mg/kg/day ± 11.7 (mean ± SD); the mean 10-monohydroxide level was 23.1 μg/mL ± 8.6 (mean ± SD). Seizures improved within 4 days of oxcarbazepine initiation in six children, whereas two children required higher doses. Their follow-up has ranged from 12 to 24 months, without seizure recurrence or serious side effects. Our patients demonstrate the efficacy of oxcarbazepine for nocturnal hyperkinetic seizures in children with nocturnal frontal-lobe epilepsy.

Raju GP, Sarco DP, Poduri A, Riviello JJ, Bergin AMR, Takeoka M. Oxcarbazepine in children with nocturnal frontal-lobe epilepsy. Pediatr Neurol 2007;37:345-349.

Introduction

Nocturnal frontal-lobe epilepsy (NFLE) is a distinct partial epilepsy syndrome within the spectrum of paroxysmal sleep-related disturbances. Three distinct subtypes of clinical seizures are seen in patients with NFLE: paroxysmal arousals, nocturnal motor seizures with dystonic or hyperkinetic features, and episodic nocturnal wanderings [1-3]. Paroxysmal arousals are recurrent, abrupt arousals from nonrapid eye movement sleep with occasional stereotyped motor behaviors, typically lasting <20 seconds. Nocturnal paroxysmal events consist of dystonic or dyskinetic movements of the head, trunk, or limbs with vocalization, of a duration between 20 seconds and 2 minutes. Episodic nocturnal wanderings occur in <40% of patients with NFLE, typically last between 1-3 minutes, and are best characterized as stereotypic, agitated somnambulism [2,4]. Combinations of all three NFLE subtypes frequently occur within the same patient.

The absence of definitive epileptiform abnormalities on interictal and sometimes ictal scalp electroencephalogram (EEG) recordings in patients with NFLE may result in misdiagnoses, including dystonia, or a parasomnia, such as night terrors or somnambulism. The use of video polysomnography, in addition to zygomatic and sphenoidal EEG electrodes, demonstrated that the clinical events seen in patients with NFLE are seizures with frontal-lobe onset [5]. Although there is no agreement on the standard for the diagnosis of NFLE, long-term video and ictal EEG monitoring provides more direct evidence than video polysomnography that these nocturnal events are epileptic in origin, when such ictal EEG changes are identified.

Carbamazepine was demonstrated to be efficacious at low doses in some patients with NFLE [1]. However, only a minority of these patients respond completely, and 32%

From the *Department of Neurology and †Division of Epilepsy and Clinical Neurophysiology, Children's Hospital Boston, and Department of Neurology, Harvard Medical School, Boston, Massachusetts.

Communications should be addressed to:
Dr. Takeoka; Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Children's Hospital Boston, Fegan 9; 300 Longwood Ave.;
Boston, MA 02115.
E-mail: masanori.takeoka@childrens.harvard.edu
Received January 16, 2007; accepted June 13, 2007.

doi:10.1016/j.pediatrneurol.2007.06.013 • 0887-8994/07/$—see front matter

Table 1. Clinical profile of patients with nocturnal frontal-lobe epilepsy

Patient	Sex	Age of onset	Seizure type	Daytime events	Family history	Magnetic resonance imaging results
1	F	5.5 years	H	Rare	No	Normal
2	M	12.5 years	H	Rare	No	Normal
3	M	7 years	H	No	No	Mild ventriculomegaly
4	M	4 years	H	No	No	Normal
5	M	6 years	H, CA	Rare	N/A	Normal
6	F	16 years	H	No	Yes	Normal
7	M	9 years	H	No	No	Normal
8	F	4.5 years	H, CA	Rare	Yes	Normal

Abbreviations:
CA = Confusional arousal
H = Hyperkinetic
L = Left
RAHM = Rapid alternating hand movements

are resistant to carbamazepine and all other antiepileptic drugs used [6,7]. In this study, we report on the use of oxcarbazepine in eight children with NFLE, six of whom failed other antiepileptic medications, including one patient who failed carbamazepine.

Methods

The study was approved by the Institutional Review Board of Children's Hospital Boston. Eight patients, all under the care of the authors at Children's Hospital Boston, were consecutively identified over a 2-year period from 2004-2006, and their medical records were retrospectively reviewed. Seizures were characterized clinically as brief, stereotypical, nocturnal hyperkinetic movements, often associated with vocalizations. No patients identified with this condition were excluded from our analysis. Routine EEG, prolonged, continuous video EEG telemetry, and brain magnetic resonance imaging had been performed in all eight children. Baseline seizure frequency was estimated from parental reports and calculated from prolonged, continuous video EEG telemetry, performed before oxcarbazepine treatment. We analyzed the semiology, response of seizures to medication by parental report, side effects, and routine blood tests, including complete blood counts, electrolytes, liver enzymes, and serum 10-monohydroxide derivative levels.

Results

The children's ages ranged from 4 to 16 years. All had brief, stereotypical, nocturnal hyperkinetic movements, often associated with grunting or choking sounds which were witnessed and easily described by parental report. Interictal and ictal EEG changes, captured on prolonged, continuous video EEG telemetry, confirmed the diagnosis of NFLE by demonstrating ictal EEG discharges originating from the frontal lobes. Whereas three children (Patients 1, 2, and 4) had normal interictal EEGs, all children had abnormal ictal EEGs, showing bifrontal beta activity with or without irregular rhythmic slowing.

Three children (Patients 3, 7, and 8) had right frontocentral spike-and-slow-wave complexes or slowing interictally. Their ictal EEGs indicated bifrontal beta activity or rhythmic 6-7-Hz theta activity, with right-hemisphere predominance in two children (Patients 7 and 8). Two children (Patients 5 and 6) had interictal bifrontal spikes or spike-and-wave complexes and bifrontal ictal onsets. The mean baseline seizure frequency before oxcarbazepine treatment, as determined by prolonged, continuous video EEG telemetry, was 7.7 seizures per night (range, 1.7-31.7 seizures per night).

Brain magnetic resonance imaging studies revealed no focal brain lesion in any of the children. However, one child had mild ventriculomegaly. Clinical features, magnetic resonance imaging results, and EEG findings on all cases are summarized in Table 1.

Six of the eight children were initially started on an antiepileptic drug other than oxcarbazepine, with minimal or no response in seizure control per parental report. Ineffective antiepileptic drugs in these six children included valproic acid, levetiracetam, lamotrigine, gabapentin, and phenytoin. The doses were titrated to maximum recommended doses or high therapeutic serum levels when available. These medications were discontinued if limited by side effects. Of note, Patient 6, who was treated initially with carbamazepine, reached a high therapeutic serum carbamazepine level of 11.2 μg/mL with no significant reduction in seizure frequency. Subsequent treatment with oxcarbazepine in this patient resulted in complete freedom from seizures, with a follow-up of 24 months. Two children were initially started on oxcarbazepine after characterization of the seizures as consistent with NFLE. All eight children were initiated on oxcarbazepine at 10 mg/kg/day divided equally in twice-daily dosing, and the dose was increased to standard recommended doses per weight (between 15-45 mg/kg/day).

Oxcarbazepine reduced seizure frequency within 4 days of drug initiation in six children, with complete seizure control within 2 weeks after oxcarbazepine, according to parental reports. Two children (Patients 2 and 5) required higher doses of oxcarbazepine before achieving complete

Table 1. Continued

Neurologic examination	Development	Interictal electroencephalogram	Ictal electroencephalogram onset
Normal	Normal	Normal	Bifrontal beta activity, then irregular slowing
Normal	Normal	Normal	Bifrontal irregular slowing
Mild, slow RAHM	Fine motor delay	R frontocentral spike and slow waves	Bifrontal rhythmic theta activity
Normal	Normal	Normal	Bifrontal, irregular theta activity
Normal	Normal	Bifrontal L > R bursts of spike and slow waves	Bifrontal irregular slowing
Normal	Mild learning difficulty	Bifrontal spikes	Bifrontal irregular slowing
Normal	Normal	R temporal frontal slowing and sharp waves	R > L frontal beta activity, then bifrontal irregular slowing
Normal	Normal	Mild R temporal slowing	R > L frontal beta activity, then irregular slowing

F = Female
M = Male
N/A = Not available
R = Right

seizure control. All eight children have been followed for 12-24 months without seizure recurrence. Minimal side effects were observed in two children that correlated with higher oxcarbazepine doses: dizziness and somnolence occurred in Patient 1, and diplopia in Patient 2. For the entire group, the mean oxcarbazepine dose was 30.4 ± 11.7 (mean ± SD) mg/kg/day, and 10-monohydroxide levels were 11-38 μg/mL (mean ± SD, 23.1 ± 8.6). Serum sodium levels were within normal range, except for one child with mild, asymptomatic hyponatremia at 129 mEq/L (range, 129-144 mEq/L; mean ± SD, 138.2 ± 3.0). Serum analyses of liver enzymes, complete blood counts, and electrolytes other than sodium all produced results within normal limits. Failed antiepileptic drugs, oxcarbazepine doses, and responses to oxcarbazepine for all cases are summarized in Table 2.

Discussion

Patients with NFLE present with clinical seizures that are often confused with parasomnias, such as somnambulism and night terrors, thus often delaying the diagnosis of this localization-related epilepsy. To add to the potential diagnostic confusion, the interictal EEG results are normal in 51% of reported cases of NFLE, and even the ictal EEG results are normal in 44% of these patients, further contributing to delays in diagnosis [1].

In our study, all eight children were diagnosed as having NFLE, based on clinical features including seizure semiology and ictal EEG findings on continuous video EEG telemetry. Video polysomnography was not obtained, because we thought that ictal EEG findings originating from the frontal region correlating with nocturnal hyperki-

Table 2. Response of patients with nocturnal frontal-lobe epilepsy to OXC

Patient	Previous AEDs	OXC Maximum dose (mg/kg/day)	OXC Maximum level (μg/mL)	Seizures on OXC	Side effects on OXC	Hyponatremia
1	LEV, PHT	48.2	36	None	Transient diplopia	No
2	LEV	31.6	38	None	Mild somnolence	No
3	VPA	30.0	17	None	None	No
4	VPA, GBP	37.0	18	None	None	No
5	None	23.8	13	None	None	No
6	CBZ, VPA, PHT, LTG	15.3	11	None	None	Mild (129 mEq/L)
7	None	20.4	22	None	None	No
8	VPA	21.4	N/A	None	None	N/A

Abbreviations:
CBZ = Carbamazepine
GBP = Gabapentin
LEV = Levetiracetam
LTG = Lamotrigine
N/A = Not available
OXC = Oxcarbazepine
PHT = Phenytoin
VPA = Valproic acid

netic seizures are more direct evidence for NFLE, compared with video polysomnography.

Historically, carbamazepine has been the drug of choice in patients with NFLE. In a previous study [7], carbamazepine was used in 80 patients over a 23-year period in doses ranging from 200 to 1000 mg per day. Fifty-nine patients received carbamazepine monotherapy, and 21 patients received polytherapy combining carbamazepine with other antiepileptic drugs, including phenytoin, valproic acid, clonazepam, phenobarbital, primidone, clobazam, lamotrigine, and vigabatrin. Thirty-two percent of these patients with NFLE did not respond to carbamazepine; 24% (19 patients) had a 50% reduction in seizure frequency, another 24% (19 patients) had a 75% reduction in seizure frequency, and only 20% (16 patients) had complete cessation of seizures [2]. Here, we achieved complete cessation of nocturnal seizures, based on parental report of seizure frequency, with oxcarbazepine treatment in 100% (8/8) of our NFLE patients, with a follow-up period of 12-24 months. This is in contrast to the complete cessation of nocturnal seizures with carbamazepine treatment in only 20% (19/80) of patients with NFLE in previous reports [2,6]. Because the parents of the patients detected clinical seizures before initiation of oxcarbazepine, we considered the complete resolution of seizures for a prolonged period of time (12-24 months) to be a reliable indicator of seizure freedom.

Our results demonstrate that oxcarbazepine is an efficacious and well-tolerated medication for the treatment of NFLE. In the eight children in this report, oxcarbazepine was dramatically effective in NFLE with nocturnal hyperkinetic motor seizures, with complete resolution of signs within a few weeks of initiation of oxcarbazepine. In particular, amongst other failed medications (valproic acid, phenytoin, lamotrigine), Patient 6 had also failed carbamazepine at high therapeutic serum levels, but reached complete seizure control several weeks after initiation of oxcarbazepine.

Although further studies are necessary to compare efficacy and tolerability between carbamazepine and oxcarbazepine, our study demonstrates the efficacy of oxcarbazepine in NFLE, as well as the tolerability of oxcarbazepine at higher doses. Although carbamazepine and oxcarbazepine are related drugs, we think that our preliminary data from these eight patients suggest that oxcarbazepine might be more efficacious than carbamazepine, considering previously published reports [2]. However, head-to-head trials are needed to confirm this finding. Many children do not tolerate higher doses of carbamazepine, yet will tolerate oxcarbazepine at higher doses, making oxcarbazepine a more suitable medication in some younger patients with NFLE. The differences between the 10,11-epoxide metabolite of carbamazepine and the 10-monohydroxide metabolite of oxcarbazepine may account for the better tolerability of oxcarbazepine [8]. One child had mild asymptomatic hyponatremia, and the observed clinical side effects in other children were minimal, transient, and dose-dependent, and improved with lower serum 10-monohydroxide levels. From our experience, both the efficacy and tolerability of oxcarbazepine suggest that oxcarbazepine should be considered as a potential treatment for NFLE.

Clinical and electrophysiologic characteristics of nonfamilial NFLE and autosomal-dominant NFLE syndrome are indistinguishable. Autosomal-dominant NFLE is a heterogeneous genetic disorder [9,10], and it is estimated that neuronal nicotinic acetylcholine receptor subunit CHRNA4 and CHRNB2 mutations account for 20-30% of patients with a positive family history of NFLE, and $<5\%$ of patients with a negative family history for NFLE [11]. We have not determined the mutation status of the CHRNA4 and CHRNB2 genes in our group, but only one of the eight children had a family history of seizures, which suggests that we are less likely to find a mutation in these two nicotinic acetylcholine receptor subunits.

Future studies correlating such genetic mutations in patients with NFLE may suggest insights into the pathophysiology of NFLE, such as the involvement of nicotinic acetylcholine receptors. Acetazolamide and nicotine were demonstrated to be effective in NFLE, but no extensive controlled trials have been performed to confirm such findings [12,13]. Recently, the use of topiramate in 24 patients with NFLE, with a follow-up period of 6 months to 6 years, was described [14]. In this study, topiramate as monotherapy or add-on therapy resulted in a 50% reduction in seizure frequency in 62.5% (15 patients), with complete seizure cessation in 25% (6 patients), as determined by the use of patient seizure diaries. None of the eight patients with NFLE in our series had been treated with topiramate. However, the use of oxcarbazepine alone or in combination with topiramate may be of use in a subset of drug-resistant patients with NFLE, and requires further investigation. Carbamazepine was reported to have noncompetitive inhibitory effects on nicotinic acetylcholine receptors [15]. Particular mutations in these acetylcholine receptors may alter their sensitivity to certain antagonists such as carbamazepine [16]. Such effects on acetylcholine receptor sensitivity may be expected because of a similar molecular conformation in oxcarbazepine, but have yet to be demonstrated. Additional studies will be necessary to assess these potential mechanisms of oxcarbazepine's efficacy in patients with NFLE.

Conclusions

Our experience indicates that oxcarbazepine was very effective for NFLE in our treated patients with primarily hyperkinetic motor seizures. All eight children tolerated treatment with oxcarbazepine, without significant side effects. The majority of these children were treated unsuccessfully with other antiepileptic medications prior to oxcarbazepine. Prospective studies will be necessary to establish more firmly the efficacy of oxcarbazepine in NFLE. In addition, head-to-head comparisons between

oxcarbazepine and other antiepileptic drugs will be needed to prove objectively that oxcarbazepine is more effective in patients with NFLE.

This work was presented in December 2005 at the Annual Meeting of the American Epilepsy Society in Washington, DC.

References

[1] **Oldani** A, Zucconi M, Asselta R, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain 1998;121:205-23.

[2] **Provini** F, Plazzi G, Tinuper P, Vandi S, Lugaresi E, Montagna P. Nocturnal frontal lobe epilepsy. A clinical and polygraphic overview of 100 consecutive patients. Brain 1999;122:1017-31.

[3] **Combi** R, Dalpra L, Tenchini ML, Ferini-Strambi L. Autosomal dominant nocturnal frontal lobe epilepsy. A critical overview. J Neurol 2004;251:923-34.

[4] **Pedley** TA, Guilleminault C. Episodic nocturnal wanderings responsive to anticonvulsive drug therapy. Ann Neurol 1977;2:30-5.

[5] **Tinuper** P, Cerullo A, Cirignotta F, Cortelli P, Lugaresi E, Montagna P. Nocturnal paroxysmal dystonia with short-lasting attacks: Three cases with evidence for an epileptic frontal lobe origin of seizure. Epilepsia 1990;31:549-56.

[6] **Lugaresi** E, Cirignotti F, Montagna P. Nocturnal paroxysmal dystonia. J Neurol Neurosurg Psychiatry 1986;49:375-80.

[7] **Provini** F, Plazzi G, Montagna P, Lugaresi E. The wide clinical spectrum of nocturnal frontal lobe epilepsy. Sleep Med Rev 2000;4: 375-86.

[8] **Schmidt** D, Elger CE. What is the evidence that oxcarbazepine and carbamazepine are distinctly different antiepileptic drugs? Epilepsy Behav 2004;5:627-35.

[9] **Steinlein** OK, Mulley JC, Propping P, et al. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet 1995;11:201-3.

[10] **Steinlein** OK. Molecular biology in autosomal dominant nocturnal frontal lobe epilepsy. In: Berkovic SF, Genton P, Hirsch E, Picard F, eds. Genetics of focal epilepsies. London: John Libbey and Co., 1999;187-202.

[11] **Berkovic** SF, Scheffer IE. Autosomal dominant nocturnal frontal lobe epilepsy. Gene reviews. GeneTests (www.genetests.org). Seattle 2004.

[12] **Varadkhar** S, Duncan SJ, Cross H. Acetazolamide and autosomal dominant frontal lobe epilepsy. Epilepsia 2003;44:986-7.

[13] **Willoughby** JO, Pope KJ, Eaton V. Nicotine as an antiepileptic agent in ADNFLE. Epilepsia 2003;44:1238-40.

[14] **Oldani** A, Manconi M, Zucconi M, Martinelli C, Ferini-Strambi L. Topiramate treatment for nocturnal frontal lobe epilepsy. Seizure 2006;15:649-52.

[15] **Ortells** MO, Barrantes GE. Molecular modeling of the interactions of carbamazepine and a nicotinic receptor involved in the autosomal dominant nocturnal frontal lobe epilepsy. Br J Pharmacol 2002;136: 883-95.

[16] **Picard** F, Bertrand S, Steinlein OK, Bertrand D. Mutated nicotinic receptors responsible for autosomal dominant nocturnal frontal lobe epilepsy are more sensitive to carbamazepine. Epilepsia 1999;40: 1198-209.