

Experience With Lacosamide in a Series of Children With Drug-Resistant Focal Epilepsy

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We report our pediatric experience with lacosamide, a new antiepileptic drug, approved by the US Food and Drug Administration as adjunctive therapy in focal epilepsy in patients more than 17 years old. We retrospectively reviewed charts for lacosamide use and seizure frequency outcome in patients with focal epilepsy (Wilcoxon signed rank test). Sixteen patients (7 boys) were identified (median dose 275 mg daily, 4.7 mg/kg daily; mean age 14.9 years, range 8-21 years). Patients were receiving a median of 2 antiepileptic drugs (interquartile range [IQR] 1.7-3) in addition to having undergone previous epilepsy surgery ($n = 3$), vagus nerve stimulation ($n = 9$), and ketogenic diet ($n = 3$). Causes included structural (encephalomalacia and diffuse encephalitis, 1 each; stroke in 2) and genetic abnormalities (Aarskog and Rett syndromes, 1 each) or cause not known ($n = 10$). Median seizure frequency at baseline was 57 per month (IQR 7-75), and after a median follow-up of 4 months (range 1-13 months) of receiving lacosamide, it was 12.5 per month (IQR 3-75), ($P < 0.01$). Six patients (37.5%; 3 seizure free) were classified as having disease that responded to therapy ($\geq 50\%$ reduction seizure frequency) and 10 as having disease that did not respond to therapy ($< 50\%$ in 3; increase in 1; unchanged in 6). Adverse events (tics, behavioral disturbance, seizure worsening, and depression with suicidal ideation in 1 patient each) prompted lacosamide discontinuation in 4/16 (25%). This retrospective study of 16 children with drug-resistant focal epilepsy demonstrated good response to adjunctive lacosamide therapy (median seizure reduction of 39.6%; 37.5% with $\geq 50\%$ seizure reduction) without severe adverse events. © 2011 Elsevier Inc. All rights reserved.

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Introduction

Lacosamide is a new antiepileptic drug (AED) approved by the US Food and Drug Administration for adjunctive therapy in focal epilepsy in patients more than 17 years old [1]. Because of its novel mode of action of selective enhancement of the slow inactivation of voltage-gated sodium channels [2,3], it may be specifically helpful in patients who have not responded to other AEDs. There have been 1 phase II [4] and 2 phase III clinical trials with lacosamide [5,6] that demonstrated good efficacy and tolerability for treatment of focal epilepsy in subjects more than 16 years old. Some reports also provided additional indications in status epilepticus [7,8], with controlled studies revealing a similar safety and tolerability profile of the intravenous formulation to oral lacosamide [9,10].

Lacosamide has been demonstrated to have a fast onset of anticonvulsant activity and to greatly reduce focal seizures at doses of 200 to 400 mg daily as adjunct therapy in drug-resistant focal epilepsy in adults [4-6,11]. The most common adverse effect was dizziness, which was dose related and observed more in the titration period. Other effects included coordination abnormalities, vomiting, diplopia, nausea, vertigo, and blurred vision [4-6,11]. Baseline electrocardiogram was necessary because of selective dose-dependent reversible enhancement of slow

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inactivation of cardiac sodium channels inducing dose-dependent prolongation of the PR interval [2-3,12].

We report the experience with the use of oral lacosamide in children with drug-resistant focal epilepsy at a tertiary-care center, Children's Hospital Boston.

Patients and Methods

We performed a 2-year retrospective analysis (July 2008 to June 2010) of the electronic charts of the neurology outpatient and inpatient database and reviewed clinical presentation as well as outcome of children receiving lacosamide. The inclusion criteria were use of lacosamide, age up to 21 years, focal epilepsy, and assessment in the Department of Neurology, Children's Hospital Boston. The exclusion criterion was lack of follow-up visit.

Epileptic seizures were classified according to the International League Against Epilepsy [13,14]. Baseline seizure frequency was assessed over a baseline of 9 months (interquartile range [IQR] 3.7-9; mean 15.3, S.D. 23.9) and compared to treatment on lacosamide (Wilcoxon signed rank test). The number of visits in the baseline period ranged from 1 to 28 (median 2). Families completed standardized seizure diaries to recollect seizure frequency; these data were transcribed into the charts by attending physicians. A $\geq 50\%$ reduction in seizure frequency was considered a response to therapy. Statistical analyses were performed with STATA version 11 software (StataCorp, College Station, TX). The study was approved by the Institutional Review Board Committee on Clinical Investigations at Children's Hospital Boston.

Results

We identified 24 patients who received oral lacosamide. Eight patients were excluded from analysis (3 older than 21 years, 4 with inadequate clinical information, and 1 with primary generalized epilepsy).

Patients

The mean age of the 16 patients (7 boys) was 14.9 (S.D. 3.3; median 15, range 8-21) years. Epilepsy onset occurred at a mean age of 5.6 (S.D. 4.1; median 7, IQR 0.8-9.1) years. All patients had drug-resistant focal epilepsy, and 6 manifested delay in acquisition of developmental milestones according to office-visit documentation. Structural abnormalities were diagnosed in 4 patients (encephalomalacia in 1, postencephalitis diffuse atrophy in 1, and stroke in 2); 2 had a genetic syndrome (Aarskog and Rett syndromes in 1 patient each); and in 10 patients, no specific etiology was found. Median number of current AEDs was 2 (IQR 1.7-3; mean 2.3, S.D. 1.2) and of previous AEDs, 4 (IQR 2-7; mean 4.8, S.D. 3.2). Additionally, 3 patients had previously undergone resective epilepsy surgery, 8 had received a vagus nerve stimulator, and 3 had received a ketogenic diet. Two patients underwent ketogenic diet and surgery or vagus nerve stimulation, and 1 received all these 3 types of therapeutic modalities. Epileptic seizures were classified as follows: dyscognitive ($n = 10$), somatosensory auras ($n = 2$), gelastic ($n = 1$), motor ($n = 1$), versive ($n = 2$), atonic ($n = 2$), and hemiclonic ($n = 1$). Further, 8 patients with focal seizures also presented secondarily generalized tonic-clonic seizures, and isolated generalized tonic-clonic seizures occurred in 2 patients. Five patients presented with more than one seizure type.

Two patients had epileptic spasms during infancy (Table 1). An electrocardiogram report was available in 13 patients, and none revealed heart rhythm abnormalities.

Lacosamide Treatment and Follow-up Duration

Lacosamide therapy was initiated when the patient was at a median age of 15.6 (range 8-21; mean 13.6, S.D. 5.9) years. Nine patients were younger than 16 at the time of lacosamide initiation. Median lacosamide starting dose was 50 mg daily (IQR 50-100; mean 71.8, S.D. 25.6) or 1.3 mg/kg daily (IQR 0.6-1.8; mean 1.3, S.D. 0.7), and median maintenance dose was 275 mg daily (IQR 137.5-400; mean 262.5, S.D. 158.6) or 4.7 mg/kg daily (IQR 3.1-6.6; mean 4.9, S.D. 2.4) reached over a 2- to 4-week interval. Median follow-up period was 4 months (range 1-13; mean 5.4, S.D. 3.5).

Seizure Frequency at Baseline and Outcome

Median seizure frequency over a median baseline period of 9 months (IQR 3.7-12; mean 15.3, S.D. 23.9) was 57 per month (IQR 7-75; mean 104.8, S.D. 184.4) and while receiving lacosamide was 12.5 per month (IQR 3-75; mean 49.7, S.D. 77.2) ($P < 0.01$, Wilcoxon signed rank test) over a median follow-up period of 4 months (IQR 3-7.2; mean 5.3, S.D. 3.4) (Fig 1). Median seizure reduction was 39.6% (IQR 0-82.5; mean 34.8, S.D. 63.3). Six (37.5%) patients were classified as having disease responding to therapy, including 2 who had undergone previously unsuccessful epilepsy surgery. Three patients became seizure free while receiving lacosamide. Ten (62.5%) were classified as having disease not responsive to therapy: 3 of these presented with $< 50\%$ seizure reduction, 6 had no change, and 1 had an increase in seizure frequency. Four out of 16 patients could not tolerate the medication because of adverse events: 1 girl became seizure free but developed oral tics, which remitted after discontinuation of lacosamide; 1 had severe behavioral outbursts; 1 had worsening of seizures with accompanying vomiting; and 1 manifested ataxia and depression associated with suicidal ideations, which subsided after lacosamide was withdrawn. Mild transient adverse events were observed in 2 (worsening of chronic headache in 1 and nausea and blurred vision in the other). Of the 4 patients who discontinued the drug because of adverse events, one became seizure free, the second had no change in seizure frequency, the third had increasing seizures, and the last one had 37.5% seizure reduction. Of the 3 patients with follow-up of < 3 months, therapy was discontinued in 2 as a result of lack of efficacy or worsening of seizures, and the third was lost to follow-up (Table 1).

Discussion

Summary

This retrospective study of 16 children (mean age 14.9 years) with drug-resistant focal epilepsy revealed adjunctive

Table 1. Demographic and clinical data of 15 children with epilepsy treated with lacosamide

Patient No.	Sex	Age at Seizure Onset, yr	Age LCM Initiated, yr	SS	No. of Previous AEDs	Current AEDs	LCM Dose, mg/kg daily
1	F	11	16.9	DYS	1	TPM, LEV	2.9
2	F	8	17	FS, DYS, GTCS	7	OXC, ZNS, CZP	0.5
3	M	1	14.6	DYS	3	PHT, LEV	2.8
4	F	0.5	14	GTCS	12	TPM, GBP	7.2
5	F	8	14.7	DYS	2	VPA, RUF, PGB	4.1
6	F	8	17	DYS	4	LEV	5.6
7	M	10	12.9	DYS, GTCS	3	GBP	8.8
8	M	0	15.6	FM, DYS (IS in past)	5	PGB	4
9	F	1.6	12.7	GTCS, atonic	9	ZNS, RUF, LZP	8.6
10	M	9.7	16.5	Gelastc, FS, GTCS	7	VPA, OXC, RUF, CLB	3.8
11	M	10	16.5	GTCS	2	TPM, LTG, LEV, CZP	2.3
12	F	0.5	21.2	FV (IS in past)	9	CBZ, LTG	6.8
13	F	5.8	15.6	DYS, GTCS	4	PHT	5.4
14	M	6	8.4	Hemiclonic, GTCS	1	LEV, OXC	2
15	F	0.5	9.3	DYS, GTCS	6	OXC, VPA, LZP	5
16	M	8.9	17.5	FV, DYS, atonic, GTCS	3	LEV, LTG, CZP, PB	6

Abbreviations:

AED = Antiepileptic drug	GTCS = Generalized tonic-clonic seizures	PVEM = Periventricular encephalomalacia
CBZ = Carbamazepine	KD = Ketogenic diet	RSF = Reduction in seizure frequency
CLB = Clobazam	IS = Infantile spasms	RUF = Rufinamide
CZP = Clonazepam	LCM = Lacosamide	SF = Seizure frequency
DYS = Dyscognitive	LEV = Levetiracetam	SS = Seizure semiology
FM = Focal motor	LTG = Lamotrigine	TPM = Topiramate
FS = Focal somatosensory	LZP = Lorazepam	UKN = Unknown
FUP = Follow-up	OXC = Oxcarbazepine	VNS = Vagus nerve stimulation
FV = Focal versive	PGB = Pregabalin	VPA = Valproic acid
GBP = Gabapentin	PHT = Phenytoin	ZNS = Zonisamide

lacosamide administration to have good efficacy (median seizure reduction of 39.6% and 37.5% [6/16] with $\geq 50\%$ seizure reduction) without severe adverse events; 25% (4/16) had unacceptable adverse events, including a patient who manifested depression and suicidal ideation.

Previous Studies

Previous studies have reported lacosamide use in patients more than 16 years old. The median age of our patients was lower than the median age in the previously reported series [4-6] (Table 2). Lacosamide dose (median 275 mg daily, 4.7 mg/kg daily) was similar to the low-dose group (200 mg daily) in 2 of these studies [4-5]. The seizure reduction and response rate ($\geq 50\%$ seizure reduction) in our series were slightly higher than what has been previously reported in randomized clinical trials. Our study demonstrates a 39.6% seizure reduction rate and a 37.5% response rate with lacosamide in children as compared to previous studies in patients older than 16 years. These revealed seizure reduction ranging 26-40% and a response rate of 33-40.1% [4-6] (Table 2).

Pharmacokinetics

Lacosamide presents with high oral bioavailability, linear kinetics in the dose range of 100 to 800 mg, an elimination half-life of 13 hours, a primarily (95%) renal elimination [15-17], low plasma protein binding (15%), and a low potential for drug interactions; in addition, it does not induce or inhibit the cytochrome P450 enzymes [18]. This favorable pharmacokinetic profile may lead to fewer adverse events when compared to other AEDs. The mean age of the patients in our study was 14.9 (S.D. 3.3; median 15, range 8-21) years. Younger patients may have different responses based on age-specific factors, such as pharmacokinetic and pharmacodynamic properties. Nevertheless, additional studies with older children, as in the present study, are necessary to further assess safety issues.

Adverse Events

The adverse-event profile in our patients differs from the adult series. Mild adverse events such as nausea and blurred vision reported in one of our patients are commonly observed with other sodium channel modulating drugs like

Etiology	Baseline Period, mo	SF before LCM, per mo	SF after LCM, per mo	FUP, mo	RSF, %	Adverse Events	Other Therapies
UKN	5	600	6	3	90	No	Surgery
UKN	12	60	35	10	42	No	VNS
UKN	3	15	10	4	33	No	VNS
Aarskog syndrome	96	600	300	4	50	No	No
UKN	6	75	75	4	0	Chronic headache worsening	VNS
UKN	44	2	0	4	100	No	No
UKN	1	540	120	3	78	No	No
Infarct	12	60	60	1	0	No	No
UKN	1	75	15	9	80	No	VNS
Infarct	18	90	90	8	0	Nausea, diplopia, blurred vision, sedation	KD, surgery
UKN	1	54	0	6	100	No	No
PVEM	4	4	4	13	0	No	VNS
UKN	12	4	0	7	100	Tics	VNS, KD, surgery
UKN	6	0.27	0.27	2	0	Behavior problems	No
Rett syndrome	12	30	75	1	-150	Increasing seizures, vomiting	VNS
After encephalitis	12	8	5	7	37.5	Ataxia, depression, suicidal ideation	VNS, KD

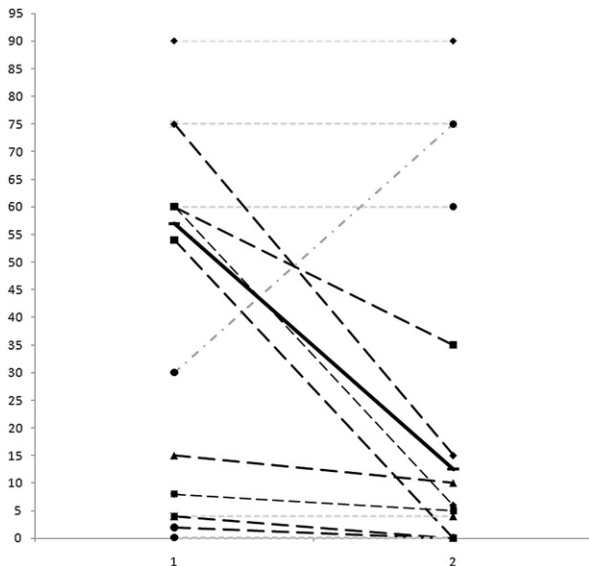


Figure 1. Seizure frequency (per month) before and after initiation of lacosamide therapy. Individual dashed lines represent seizure frequency of individual patients; the solid line represents median frequency before (1) and after (2) lacosamide treatment. Five patients experienced no change in seizure frequency, 1 patient experienced an increase, and the remaining patients experienced improvement in their seizure frequency. Data from 2 patients with outlying data are not illustrated, but they experienced improvement in their seizure frequency.

carbamazepine and phenytoin as well other drugs affecting the central nervous system. Worsening of seizure frequency as seen in one of our patients has also been reported with other AEDs [19]. Additionally, behavioral disturbances have also been observed with other AEDs such as levetiracetam [20].

One of our patients reported new onset of oral tics. Dyskinesia is rarely associated with AED use [21,22]. Zaccara et al. found 130 case descriptions of dyskinesias after the use of AED, mostly related to the older AEDs such as phenytoin [23]. Frequently, patients had received more than one type of AED. Although new AEDs are less likely to cause such adverse events, some reports of movement disorders associated with lamotrigine and tiagabine have been published [24,25]. Onset of tics after initiation of lacosamide and improvement after its discontinuation suggests a causal relationship.

One of our patients (17.5 years old) experienced depression associated with suicidal ideation after receiving lacosamide (400 mg daily, 6 mg/kg daily), which subsided when the drug was discontinued. The risk of suicidal behavior with the use of AEDs has been addressed in 2 recent articles that did not find increased risk in patients with epilepsy [26], except with the use of new AEDs that have

Table 2. Summary of randomized clinical trials with lacosamide compared to the present retrospective observational study

Study	n	Dose	Age, y, Mean (S.D.) Range	Median Seizure Reduction	50% Response Rate	Adverse Events	Completed Study, n (%)
Ben-Menachem et al., 2007 [4], prospective randomized controlled phase II (placebo n = 97)	107	200 mg daily	39.9 (11.7) 18-65	26% per 28 days	33%	Dizziness, nausea, fatigue, ataxia, abnormal vision, diplopia, nystagmus	312 (97.1%)
	108	400 mg daily	41.2 (11.6) 18-68	39% per 28 days	41%		
	106	600 mg daily	39.4 (10.5) 18-64	40% per 28 days	38%		
Halász et al., 2009 [5], prospective randomized controlled phase III (placebo n = 163)	163	200 mg daily	36.9 (11.7) 16-66	35.3% per 28 days	40.5%	Dizziness, nausea, vomiting	435 (89.7%)
	159	400 mg daily	37.9 (12.9) 16-70	36.4% per 28 days	35%		
Chung et al., 2010 [6], prospective randomized controlled phase III (placebo n = 104)	204	400 mg daily	39.1 (12.3) 17-71	37.3% per 28 days	38.30%	Dizziness, nausea, vomiting	316 (78%)
	97	600 mg daily	36.8 (11.7) 16-69	37.8% per 28 days	41.20%		
Present study, retrospective, observational	16	Median 275 mg daily or 4.7 mg/kg daily	13.6 (5.9) 08-21	39.6% per mo 4 mo (median follow-up)	37.5%	Oral tics, behavior problems, seizure increasing, chronic headache worsening, nausea, blurred vision, depression, suicidal ideation	12 (75%)

potential for causing depression (levetiracetam, tiagabine, topiramate, and vigabatrin) [27]. In published clinical trials with lacosamide in patients older than 16, depression and suicidal behavior were not reported [4-6].

Cardiac arrhythmias were not reported in our patients during a median follow-up of 4 months. Although lacosamide exerts a selective enhancement of slow inactivation of the sodium channels, this effect seems to be dose dependent and reversible in cardiac muscle [2]. There has been a recent report of a 37-year-old woman with epilepsy and no risk for cardiac disease who, 3 months after initiating oral lacosamide (up to 600 mg daily), sought care for acute atrial fibrillation. This resolved completely after lacosamide discontinuation [28]. In a clinical trial on the use of lacosamide for the treatment of pain, a dose-dependent small prolongation of the mean PR interval and a slight increase in mean QRS duration was observed in a patient with diabetes [29]. There is a single adult case report of a suicide attempt while receiving multiple AEDs. Included in the attempt was a massive overdose of lacosamide (12 g, 153.8 mg/kg) that resulted in a reversible prolongation of the PR interval [30].

To date, to our knowledge, no studies have reported the efficacy and tolerability of lacosamide in children with drug-resistant focal epilepsy. Our data need to be interpreted in the setting of their acquisition, including retrospective analysis, small sample size, selection, and referral and information bias, as well as seizure count and adverse events based

on parental reports. Although its safety and efficacy seems to reveal a favorable profile in clinical trials and in postmarketing studies, additional data are necessary to confirm these findings in other patient populations [31,32].

Conclusion

In this series of 16 children with treatment drug-resistant focal epilepsy and with a mean age of 14.9 years (range 8-21 years) and a median follow-up of 4 months, lacosamide administration led to a median seizure reduction of 39.6%, with 37.5% of the patients demonstrating a $\geq 50\%$ reduction in seizure frequency and no severe adverse events observed. A prospective multicenter study in children is needed to validate our observations.

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