JPPT

BRIEF REVIEW ARTICLE

Use of Lacosamide in Children with Refractory Epilepsy

Marcia L. Buck, PharmD[1,2] and Howard P. Goodkin, MD, PhD[2,3]

Departments of [1]Pharmacy Services, [2]Pediatrics, and [3]Neurology, University of Virginia, Charlottesville, Virginia

OBJECTIVES Lacosamide was approved by the US Food and Drug Administration in 2008 for adjunctive therapy for focal onset seizures in patients 17 years of age and older. The efficacy of this agent in adults has led clinicians to consider lacosamide for children with refractory seizures.

METHODS The MEDLINE database (1950-June 2012) was searched for abstracts containing lacosamide as the key term. Additional references were obtained from the manufacturer and the bibliographies of the articles reviewed. All available English-language case reports and clinical trials were included in the evaluation.

RESULTS Several case series studies have been published which support the use of lacosamide in children with refractory seizures. In the papers published to date, 30% to 50% of children experienced at least a 50% reduction in seizure frequency, similar to results obtained in clinical trials in adults. Children with focal onset seizures were most likely to benefit from treatment, while results in children with generalized seizures or multiple seizure types were mixed. Adverse effects in children were similar to those seen in adults, with dizziness, headache, and nausea occurring most frequently. Lack of efficacy has been the most common cause of discontinuation.

CONCLUSIONS Lacosamide appears to be a useful adjunct therapy in children with refractory seizures. Clinical trials are under way that may provide more definitive information on the efficacy and safety of lacosamide in children and allow clinicians to determine the appropriate place of this antiseizure drug in pediatric epilepsy management.

INDEX TERMS child, epilepsy, lacosamide, Lennox-Gastaut syndrome, partial-onset seizures

J Pediatr Pharmacol Ther 2012;17(3):211–219

INTRODUCTION

Lacosamide (Vimpat, UCB, Inc., Smyrna, GA) was approved by the United States Food and Drug Administration (FDA) on October 28, 2008, for use as an adjunctive agent in the treatment of focal onset seizures in patients 17 years of age and older.[1–3] Its unique mechanism of action, lack of significant drug interactions, relatively mild adverse effect profile, and availability in an intravenous (IV) dosage form have made lacosamide a useful addition to treatment with traditional antiseizure drugs.[3] While not yet approved for use in the pediatric population, preliminary reports suggest it may have a role in the management of refractory epilepsy (seizures not controlled with one to three antiseizure drugs). This review summarizes information in the current literature and provides preliminary recommendations for lacosamide use in children.

MECHANISM OF ACTION

Lacosamide, (*R*)-2-acetamido-*N*-benzyl-3-methoxypropionamide (Figure 1), is a functionalized amino acid that selectively enhances slow inactivation of voltage-gated sodium channels, increasing the proportion of sodium channels unavailable for depolarization. This enhancement of the slow inactivation of the voltage-gated sodium channels produces stabilization of neuronal membranes and inhibition of sustained repetitive neuronal firing (Figure 2). Unlike other anticonvulsants, including carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, and topiramate, lacosamide does not alter fast

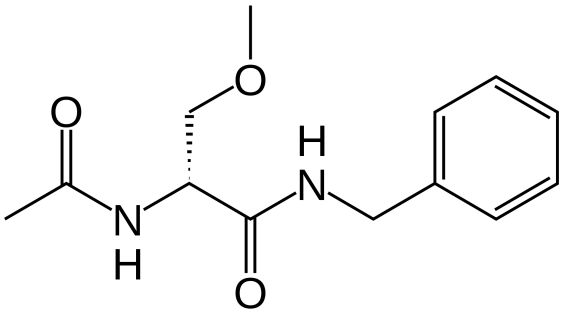

Figure 1. Chemical Structure of Lacosamide [(*R*)-2-acetamido-*N*-benzyl-3-methoxypropionamide]

inactivation of voltage-gated sodium channels. Lacosamide may also interact with collapsin response mediator protein 2 (CRMP-2);[4] however, this binding has recently been challenged.[5] CRMP-2 is part of a signal transduction cascade of neurotrophic factors involved in neuronal differentiation, regulation of gene expression, polarization, and axonal outgrowth. It has been proposed that binding at CRMP-2 could produce a neuroprotective effect, reducing glutamate-induced excitotoxicity and enhancing the clinical efficacy of lacosamide.

FORMULATION

Lacosamide is available as an injection for IV administration, as well as in tablet and oral solution forms. The 200 mg/20 mL single-dose vial contains sodium chloride and water as inactive ingredients. The pH is adjusted to achieve a pH between 3.5 and 5 with hydrochloric acid. Oral lacosamide is available in 50-, 100-, 150-, and 200-mg tablets. Inactive ingredients include colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, hypromellose, magnesium state, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and red, black, or yellow iron oxide and FD&C Blue no. 2 or indigo carmine aluminum lake as coloring agents. The 10 mg/mL strawberry-flavored lacosamide oral solution contains water, sorbitol, glycerin, polyethylene glycol, carboxymethylcellulose sodium, acesulfame potassium, methylparaben, anhydrous citric acid, sodium chloride, aspartame, and maltol.[3]

PHARMACOKINETICS

A study of the pharmacokinetic profile of lacosamide in children is currently under way. The phase 2 trial (clinical trial NCT00938431) is a multicenter study of children between 1 month and 17 years of age.[6] Patients will be randomized to receive lacosamide oral solution at doses ranging from 8 to 12 mg/kg/day. In adults, lacosamide is completely absorbed after oral administration, with a bioavailability of approximately 100%.[2,3] Food does not alter the rate or extent of absorption. Maximum serum concentrations occur 0.5 to 4 hours after an oral dose. The volume of distribution of lacosamide is approximately 0.6 L/kg. Most studies suggest a low degree of protein binding (approximately 15%).

The elimination half-life of lacosamide in adults ranges from 12 to 16 hours. An estimated 40% of the lacosamide dose is excreted as unchanged drug; conversion to *O*-desmethyllacosamide, an inactive metabolite, by CYP2C19, CYP2C9, and CYP3A4 accounts for another 20% to 30%. Genetic polymorphism does not appear to produce clinically significant changes in lacosamide pharmacokinetics, as lacosamide doses in extensive metabolizers and poor metabolizers of CYP2C19 have produced similar plasma concentrations. Area under the concentration curve (AUC) is increased by 25% in patients with mild to moderate renal impairment (creatinine clear-

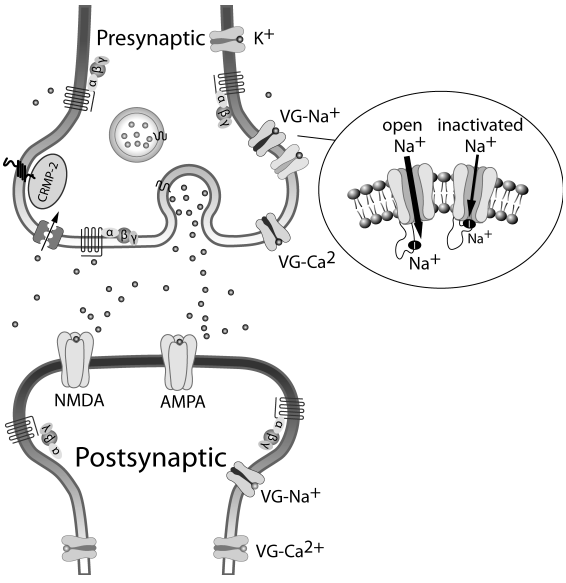

Figure 2. Mechanism of Action for Lacosamide. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; K, potassium; NMDA, N-Methyl-D-aspartic acid; VG-Ca^{2+}, voltage gates calcium channels; VG-Na+, voltage gates sodium channels

Table 1. Adverse Effects Associated with Lacosamide

Adverse Effect*	Incidence of Effect	
	Lacosamide (n=944)	Placebo (n=364)
Dizziness	31%	8%
Headache	13%	9%
Diplopia	11%	2%
Nausea	11%	4%
Vomiting	9%	3%
Fatigue	9%	6%
Blurred vision	8%	3%
Ataxia	8%	2%
Somnolence	7%	5%
Tremor	7%	4%
Nystagmus	5%	4%

** Adverse effects reported in ≥5% of patients*

ance, 30-80 mL/min) and by 60% in those with severe renal impairment (creatinine clearance, ≤30 mL/min). In patients with moderate hepatic impairment (Child-Pugh class B), the AUC of lacosamide is increased by approximately 50% to 60%. Lacosamide has not been studied in patients with severe hepatic impairment.

ADVERSE EFFECTS

Lacosamide is generally well tolerated. In pooled data from placebo-controlled clinical trials in adults, the most frequent reactions were dizziness, headache, diplopia, and nausea (Table 1).[3,7,8] Most adverse effects seen with lacosamide are dose-related and are reversible upon discontinuation or dose reduction. Discontinuation of therapy as the result of an adverse effect has been reported in 8% of adults receiving 200 mg/day, 17% of those taking 400 mg/day, and 29% of patients taking 600 mg/day.[3] Intravenous administration of lacosamide has been associated with injection site pain or discomfort in 2.5% of patients, venous irritation in 1%, and erythema in 0.5%. Similar adverse effect data have been observed in pediatric case reports and case series, with dizziness and nausea being the commonly reported reactions (Table 2). In addition to the somnolence, dizziness, and headache observed in both children and adults, the four available pediatric case series have also reported central nervous system findings of irritability, oral tics, and prolonged crying.[9–12]

Elevations in alanine transaminase up to three times the upper limit of normal were reported in 0.7% of adults receiving lacosamide in premarketing clinical trials.[3] Those changes resolved with discontinuation of therapy. A healthy adult volunteer enrolled in a clinical trial experienced acute hepatitis, with transaminase concentrations more than 20 times the upper limit of normal, and nephritis 10 days after stopping lacosamide, consistent with a delayed multiorgan hypersensitivity reaction. The patient recovered within a month with no apparent sequelae. Two other cases of rash with concurrent increased serum transaminase concentrations have been reported to the manufacturer, as well as a patient who developed myocarditis and hepatitis after starting lacosamide.[3] Hypersensitivity to lacosamide has also presented as acute angioedema in adults being treated for refractory status epilepticus.[13] There have been no reports of abnormalities in serum transaminases or angioedema in children treated with lacosamide, but one case of facial edema has been documented,[12] and close monitoring is warranted in any patient suspected of having a lacosamide-induced hypersensitivity reaction.

Lacosamide has been shown to produce a dose-related increase in the PR interval during electrocardiographic (ECG) monitoring in both healthy volunteers and patients with epilepsy.[3,7,8,14,15] This effect is likely the result of lacosamide enhancement of slow inactivation of voltage-gated sodium channels. The change appears to be proportional to the lacosamide dose, with a maximum increase of 7.3 ms in patients taking 400 mg/day and 11.9 ms in those taking 800 mg/day. Asymptomatic first-degree atrioventricular (AV) block was reported in 0.4% of adults with focal onset epilepsy and in 0.5% of adults with diabetic neuropathy participating in premarketing clinical trials. Second- or third-degree AV block has been identified in only a small number of patients, with most cases coming from postmarketing reports in adults being treated for diabetic neuropathy. A case of second-degree AV block in a patient with epilepsy was recently described.[15] The patient, a 45-year-old man, was admitted with palpitations, dyspnea, and exercise intolerance. His medications included desmopressin, hydrocortisone, levothyroxine, somatropin, alfuzosin, risedronate, carbamazepine, oxcarbazepine, and lacosamide, 200 mg once daily. Lacosamide had

Table 2. Pediatric Lacosamide Case Series and Retrospective Studies[8-11]

Study	No. of Patients Age (range)	Seizure Type	Patients experiencing ≥50% reduction in seizure frequency	Patients who discontinued therapy (%)	Mean Effective Dosage (mg/kg/day) (range)	Adverse effects reported during treatment (%)
Gavatha et al[9]	14 (3-18 yr)	Focal onset	5 (36%)	12 (67%) due to lack of efficacy at initial assessment 1 (6%) due to ADE	6.34 (1.7-10)	Somnolence (17%), irritability (11%), sleep disturbances (6%), pancytopenia (6%)
Guilhoto et al[10]	16 (8-21 yr)	Focal onset	6 (37.5%)	2 (12.5%) due to lack of efficacy 4 (25%) due to ADE	4.7 (0.5-8.8)	Nausea and vomiting (12.5%), headache (6%), blurred vision (6%), tics (6%), behavioral outbursts (6%), ataxia(6%), and depression (6%)
Heyman et al[11]	17 (1.5-16 yr)	Focal onset, tonic, generalized tonic-clonic*	6 (35%)	6 (35%) due to lack of efficacy	12.39 (6.7-20)	Nausea (18%), dizziness (18%), restlessness (12%), fatigue (12%), headache (12%), increased appetite (6%), prolonged crying (6%)
Rastogi et al[12]	16 (1-16 yr)	Focal, atonic, tonic, tonic, clonic, myolonic, atypical absence*	8 (50%)	NR	9.4 (2.4-19.4)	nausea, vomiting, gastrointestinal intolerance, dizziness, headache, somnolence, facial edema (frequency not specified)

ADE, adverse drug event; NR, not reported
** Included patients with Lennox-Gastaut syndrome (LGS)*

been initiated 3 months earlier as a replacement for zonisamide. Cardiac monitoring revealed a prolonged PR interval (>400 ms at maximum), an AV block (Mobitz I/Wenckebach), and right bundle branch block. His rhythm disturbances resolved 19 hours after his last dose of lacosamide. Zonisamide was restarted, and the patient recovered without sequelae. The authors concluded that the patient's carbamazepine may have already lengthened the PR interval to the upper limit of normal (200 ms) and the addition of lacosamide potentiated the effect. As a result of these reports, it is recommended that lacosamide be used with caution in adults with cardiac conduction problems or severe cardiac disease. In those patients, an ECG should be obtained prior to starting therapy and at the end of dose titration. Concurrent administration of other drugs that prolong the PR interval should be avoided. Although no cases of lacosamide-induced PR prolongation or AV block have been reported in children, the same precautions should apply. In addition, children with a family history of cardiac disease or conduction disturbances may be at higher risk for PR prolongation and should be closely monitored during treatment.

Suicidal thoughts have been described in patients taking antiseizure drugs. To date, a single child, age 17.5 years, who was being treated with levetiracetam, lamotrigine, clonazepam, and phenobarbital developed suicidal ideation following initiation of lacosamide that resolved after lacosamide was withdrawn.[10] In order to educate patients and their families about this risk, the FDA has approved a Risk Evaluation and Mitigation Strategy (REMS) program for all drugs in this therapeutic class.[3] A medication guide must be given to the patient or family at the time an antiseizure drug is dispensed.

Patients and their families should also be

aware that large doses of lacosamide (300-800 mg in adults) can produce a mild euphoria.[2,3] Although euphoria has been reported in less than 1% of patients enrolled in clinical trials, the risk for abuse resulted in lacosamide being approved as a schedule V controlled substance in the United States.

Given its possible interaction with CRMP-2, it has been suggested that lacosamide has the potential to adversely affect central nervous system development. CRMP-2 is known to be highly expressed during gestation and early in life.[16] Studies in rats given lacosamide early in life resulted in decreased brain weight and long-term deficits in learning and memory.[3] Administration to rats during pregnancy resulted in increased perinatal mortality and impaired growth. Additional research in this area is needed to clarify the risk-to-benefit ratio of using this therapy in infants or during pregnancy and lactation.

Lacosamide should only be used during pregnancy if no safer alternatives are available. Clinicians are encouraged to enroll any pregnant women taking lacosamide into the UCB Antiepileptic Drug Pregnancy Registry (phone, 1-888-233-2334, or website at http://www.vimpat.com).[3] Women taking lacosamide during pregnancy should also be enrolled in the North American Antiepileptic Drug Pregnancy Registry. Information on this collaborative program can be obtained by calling 1-888-233-2334 or at the website at http://www.aedpregnancyregistry.org.

DRUG INTERACTIONS

At this time, no clinically significant drug interactions with lacosamide have been identified. Lacosamide does not appear to produce significant induction or inhibition of CYP1A2, 2B6, 2C9, 2C19, or 3A4. A small (20%) increase in ethinyl estradiol has been reported in women taking lacosamide with oral contraceptives. Minor reductions in serum concentrations (< 25%) occur in carbamazepine, phenytoin, and phenobarbital when given with lacosamide.[3] None of these changes in drug concentrations require dosage adjustment. Novy and colleagues[17] recently reported a series of seven patients who developed neurologic adverse effects after lacosamide was added to a regimen containing other voltage-gated sodium channels-blocking antiseizure drugs. There was no evidence of a pharmacokinetic drug interaction or elevated serum drug concentrations in these patients that might have explained the increased incidence of diplopia, dizziness, and drowsiness. Reduction in the patient's original antiseizure drugs resulted in symptomatic improvement in all of the cases. These and other authors have proposed that adverse effects noted during lacosamide titration may represent a pharmacodynamic drug interaction resulting from synergistic voltage-gated sodium channels blockade, similar to that noted with other combinations of antiseizure drugs affecting these channels such as carbamazepine and lamotrigine.[17–19]

CLINICAL EXPERIENCE IN CHILDREN

In randomized controlled trials conducted in adults, lacosamide has demonstrated significant benefit in treating refractory seizures, with 30% to 40% of patients achieving a ≥50% reduction in seizure frequency at doses of 400 to 600 mg/day.[2,7,8] Since 2010, four studies have been published that describe similar benefits from lacosamide in children and young adults with refractory epilepsy (Table 2).[9–12]

In the first prospective case series, 14 patients between 3 and 18 years of age with focal onset seizures were treated with oral lacosamide for a period of at least 3 months.[9] All of the children had been treated with multiple antiseizure drugs prior to starting lacosamide; the average number of previously failed agents was seven, with a range from three to sixteen. Lacosamide was initiated at 1 mg/kg/day and increased in 1 mg/kg/day increments on a weekly basis. Final doses ranged from 2 to 10 mg/kg/day. Thirty-six percent (5 of 14) of the children experienced a ≥50% reduction in seizure frequency at the time of initial assessment, which ranged from 3 to 8 months (mean, 5 months). Twenty percent (3 of 14) of patients maintained this level of seizure control for an additional 8 to 13 months. In total, 1 year after enrollment, only 4 of the original 18 children were still taking the therapy. Lacosamide was eventually discontinued in 12 patients due to lack of efficacy or loss of efficacy at follow-up. One patient was lost to follow-up. Mild adverse effects were common, with 39% of children experiencing symptoms of somnolence or irritability. Only 1 patient discontinued therapy after developing normochromic anemia with

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.