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Brief Review Article

Use of Lacosamide in Children with Refractory Epilepsy

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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

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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

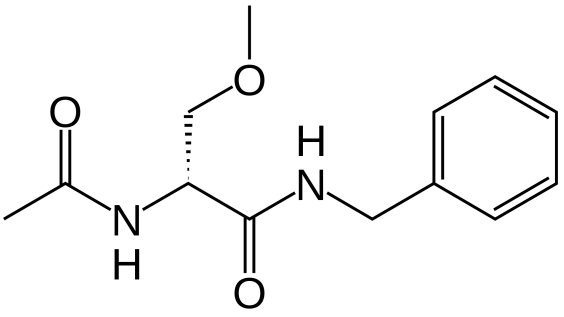

Figure 1. Chemical Structure of Lacosamide [(*R*)-2-acetamido-*N*-benzyl-3-methoxypropionamide]

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-

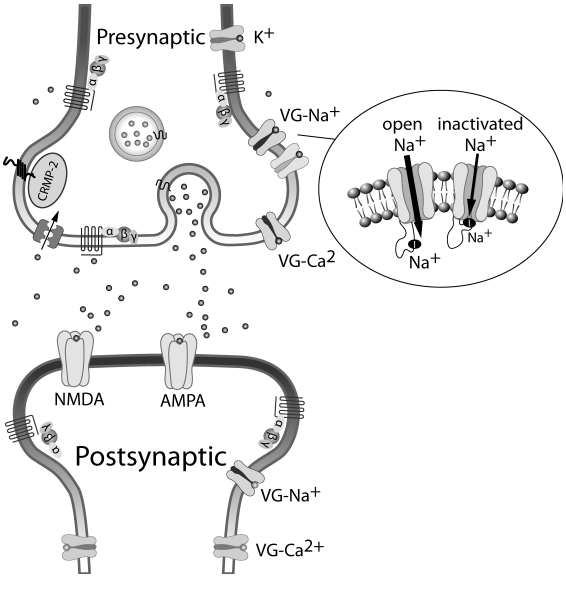

Figure 2. Mechanism of Action for Lacosamide.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; K, potassium; NMDA, N-Methyl-D-aspartic acid; VG-Ca^{2+}, voltage gates calcium channels; VG-Na+, voltage gates sodium channels

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

thrombocytopenia and granulocytopenia while receiving therapy but had a similar history of pancytopenia prior to initiation of lacosamide. After a period of worsening seizure frequency, lacosamide was restarted without any adverse effect on blood counts. Although a significant reduction in seizure frequency was not maintained in most of the patients, the authors concluded that lacosamide has the potential to be a useful adjunct therapeutic agent in children with refractory seizures.

A retrospective review was composed of a final cohort of 16 patients who were receiving an average of two other antiseizure drugs for their refractory focal onset seizures at the time lacosamide was initiated.[10] The patients ranged from 8 to 21 years old, with a mean age of 14.9 years. Two of the patients were over 17 years of age. Three patients had undergone epilepsy surgery, 9 received vagus nerve stimulation, and 3 had been treated with the ketogenic diet. The average lacosamide dose at the end of titration was 4.7 mg/kg/day. Length of follow-up ranged from 1 to 13 months, with a median of 4 months. The median number of seizures per month for the total population decreased from 57 at baseline to 12.5 at follow-up (a 39.6% reduction, $p<0.01$). Six children (37.5%) had a ≥50% reduction in seizure frequency. Three of these 6 patients were free of seizures. Seven patients had no improvement. Four patients discontinued therapy because of adverse effects, including tics, behavioral changes, increased seizures, or depression with suicidal ideation (each in 1 patient). As with the previous case series, the authors suggested that lacosamide may play a useful role in treating refractory seizures in children and should be evaluated in a prospective controlled trial.

In a retrospective study of 17 children (ages 1.5-16 years) receiving oral lacosamide for refractory seizures, 35% (6 of 17) achieved a reduction in seizure frequency of ≥50%.[11] The patient population was composed of 12 patients with focal seizures and 5 with both focal and generalized onset seizures, including 2 children diagnosed with Lennox-Gastaut syndrome (LGS). The mean number of previous antiseizure drugs used per child was 6.6 (range, 4 to 11). Initial doses ranged from 1.4 to 5 mg/kg/day (mean, 3.04 ± 1.09 mg/kg/day). Doses were titrated at weekly intervals, up to a maximum of 6.7 to 20 mg/kg/day (mean, 12.39 ± 4.48 mg/kg/day). The mean length of follow-up was 9.1 ± 4.4 months. In addition to reduction in seizure frequency, 7 children (41%) had improvement in behavioral or motor function. While a significant number of children initially demonstrated improvement, lacosamide was eventually discontinued in 6 children (35%) because of lack of efficacy. Both of the patients with LGS experienced an increase in their seizure frequency during treatment. Adverse effects were reported in 10 patients, including nausea, dizziness, restlessness, fatigue, headache, increased appetite, and prolonged crying.

Another recent prospective study described the use of lacosamide in 21 children (ages 1 to 16 years) with both focal and generalized onset seizures.[12] Sixteen patients were included in the final analysis, with a mean age of 8.6 years. Of the eight children with a generalized-onset epilepsy syndromes, four were diagnosed with LGS. The average length of follow-up was 9.8 months. The average number of antiseizure drugs at the time of lacosamide initiation was 1.8. The patients had failed an average of 6.6 previous treatments as well as the ketogenic diet and vagal nerve stimulation. The average initial dose was 5.8 mg/kg/day. The average lacosamide dose at the end of titration was 9.4 mg/kg/day, with a range of 2.4 to 19.4 mg/kg/day. Eight patients (50%) had a reduction in seizure frequency of ≥50%. Three patients had a reduction of ≥90%. Children with focal onset seizures were the most likely to respond, while patients with generalized tonic-clonic and tonic seizures were the least likely to benefit from lacosamide. Of the 4 patients with LGS, 2 had significant improvement (≥90% reduction in frequency) and 2 had no response. Adverse effects included nausea, vomiting, dizziness, headache, somnolence, and facial edema.

Despite the positive response in the 2 patients with LGS in the study described above, the role of lacosamide in treating children and young adults with this syndrome remains undefined. A 2010 case series of 3 young adult patients (24-27 years of age) with LGS described worsening of seizure frequency after initiation of lacosamide.[18] All 3 patients had been initiated on the recommended adult dose of 50 mg/day and increased at increments of 50 mg/day each week. Two of the patients reached a final dose of 200 mg/day; 1 of these patients experienced increased seizures at 15 days and the other at 30 days from the time of the last dose increase. The

third patient developed an increase in seizure frequency at 4 days after reaching a dose of 100 mg/day. All patients returned to their baseline seizure frequency after lacosamide was discontinued. The authors hypothesized that this worsening of seizure frequency may reflect a pharmacodynamic interaction resulting from an additive or synergistic effect of lacosamide with their patient's other antiseizure drugs that block voltage gates sodium channels. In a similar case report, a 20-year-old man with LGS, who had failed treatment with phenobarbital, vigabatrin, valproic acid, clobazam, and carbamazepine, was admitted for increased seizure frequency.[20] He was treated with topiramate, levetiracetam, phenytoin, clonazepam, and risperidone. After developing signs of phenytoin-induced hepatotoxicity, he was given a trial of IV lacosamide at a dose of 200 mg/day. Within days of starting therapy, the patient began to experience an increase in tonic seizures, from an average of 4 per day to 10 per day, coinciding with a worsening of EEG findings. The patient returned to baseline within 48 hours of lacosamide discontinuation.

In contrast to those reports of the use of lacosamide in the treatment of LGS, a recent case series suggested benefit from lacosamide in 3 young adults (19-23 years of age) with juvenile myoclonic epilepsy, a form of generalized epilepsy that typically presents in late childhood.[21] One of the patients received lacosamide as single-agent therapy. The other 2 patients had lacosamide added to their current regimens (valproic acid in one and a combination of levetiracetam and lamotrigine in the other) for breakthrough seizures. All 3 patients became seizure-free on a lacosamide dose of 200 mg given twice daily. Two patients remained on therapy at the time of publication (12 and 18 months), while 1 discontinued therapy after 4 months because of fatigue, depression, and anxiety. That patient's symptoms continued after lacosamide was stopped but later abated when levetiracetam was discontinued.

Lacosamide has also been used in the management of refractory status epilepticus. Several papers describe a beneficial effect in adult patients,[22,23] but to date there have been only limited reports of its use in children.[24,25] At this time, no dosing recommendations can be made for this use in infants or children.

Issues of lacosamide efficacy, adverse effects, and dosing in children are being addressed in several ongoing clinical trials. Two open-label phase 2 clinical trials are currently enrolling children from 1 month to 17 years of age. The first (trial NCT00938431) started in October 2009 and is a multicenter study of the safety and pharmacokinetics of lacosamide in children with focal onset seizures. Children who are still experiencing seizures on stable doses of up to three other antiseizure drugs are eligible to participate. Subjects will receive lacosamide oral solution in doses of 8, 10, or 12 mg/kg/day for up to 42 days. The estimated completion date for this study is March 2013. The second study, a long-term safety and efficacy study (trial NCT00938912) began in December 2009. Subjects will be treated for up to 2 years with lacosamide oral solution at doses of 2 to 12 mg/kg/day or tablets at doses between 100 and 600 mg/day. All doses will be divided and given twice daily. The trial has an estimated completion date of October 2017. In both studies, the primary outcome measure is the frequency of treatment-related adverse effects. Secondary outcomes include change from baseline seizure frequency, plasma concentrations, and change from baseline Clinical and Caregiver Global Impression of Change scores. A third study (the NCT00832884 trial) is currently under way to evaluate the safety of IV lacosamide in children. Patients between 4 and 20 years of age with epilepsy who are unable to take oral medication are eligible for enrollment in that phase 4 study. Subjects are randomized to receive lacosamide doses of 0.7, 1.4, 2.1, or 2.9 mg/kg, up to a maximum of 200 mg. Details for the phase 2 and IV lacosamide studies are available on the clinical trials website of the National Institutes of Health.[6]

DOSING AND ADMINISTRATION

The recommended initial dose of lacosamide in patients 17 years of age and older is 50 mg administered twice daily. The dose may be increased by 100 mg/day at weekly intervals up to the usual maintenance dose of 200 to 400 mg/day. Data from clinical trials have shown that doses above 600 mg did not provide greater seizure control but were associated with a higher incidence of adverse effects. There are no established dosing recommendations for lacosamide in children at this time. Based on the available pediatric case series and retrospective reviews, a starting dose of 1 mg/kg/day, divided and given in two doses,

may be considered for initiation of therapy.[9–12] Doses should be titrated at weekly intervals, with an incremental increase of no more than 1 mg/kg/day. The effective pediatric doses in the cases and studies published to date have ranged from 4 to 12 mg/kg/day. A maximum weight-based dose for children has not yet been established, but doses of up to 20 mg/kg/day have been reported.

No dosage adjustment is needed for mild to moderate renal impairment. In adults with severe renal impairment or end-stage renal disease, the manufacturer recommends a maximum daily dose of 300 mg/day. No dosing guidelines are available for pediatric patients with renal impairment. Lacosamide is removed by hemodialysis. It is recommended that a supplemental dose of up to 50% of the maintenance dose be administered after a 4-hour hemodialysis session. A maximum daily dose of 300 mg/day is also recommended for adults with mild to moderate hepatic impairment (Child-Pugh class B). Lacosamide is not recommended for use in patients with severe hepatic impairment.

The IV and oral doses of lacosamide are equivalent. It is recommended by the manufacturer that IV doses be infused, with or without further dilution, over 30 to 60 minutes. In a recent open-label trials lacosamide infusion times as short as 15 minutes were tolerated without serious adverse effects, but a case of transient hypotension after a 15 minute infusion has been reported to the manufacturer.[3,23] Lacosamide injection is stable for at least 24 hours at room temperature when diluted with sodium chloride 0.9%, dextrose injection 5%, or Lactated Ringer's solution. Lacosamide tablets or solution may be taken with or without food. A calibrated dosing spoon or oral syringe should be used to prepare doses of lacosamide oral solution to ensure delivery of an accurate dose. The solution must be discarded after 7 weeks from the date of opening. Lacosamide oral solution contains aspartame and should be used with caution in patients with phenylketonuria. A 200-mg (20-mL) dose of the oral solution provides 0.32 mg of phenylalanine.

SUMMARY

Based on the case series studies published to date, lacosamide appears to be a useful adjunct in treatment of children with seizures refractory to traditional antiseizure drugs. The percentage of pediatric patients with focal onset seizures experiencing significant reductions in seizure frequency has been similar to results obtained in adults. The results of lacosamide use in children with generalized seizures or multiple seizure types have been mixed. Clinical trials currently underway should soon 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 seizure management.

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ABBREVIATIONS AUC, area under the concentration curve; CRMP-2, collapsin response mediator protein 2; FDA, Food and Drug Administration; IV, intravenous; LGS, Lennox-Gastaut syndrome

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