Lacosamide and Epilepsy

Jacklyn A. Harris & Julie A. Murphy

Department of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, MO, USA

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Correspondence

Jacklyn A. Harris, PharmD, BCPS, Department of Pharmacy Practice, St. Louis College of Pharmacy, 4588 Parkview Place, St. Louis, MO 63110-1088, USA.
Tel.: +314-446-8542;
Fax: +314-446-8500;
E-mail: jharris2@stlscop.edu

SUMMARY

We will review all available studies on the use of lacosamide in the treatment of partial-onset seizures. The available evidence includes two open-label studies and three randomized controlled trials evaluating the safety and efficacy of oral lacosamide. One open-label study and one randomized controlled trial evaluating the safety and tolerability of intravenous lacosamide was also identified. Lacosamide was found to be efficacious with significant reduction in seizure frequency dosed 400–600 mg daily. Moreover, its adverse drug effects were mild and infrequently reported in the literature. Findings suggest that lacosamide is an effective agent for adjunctive treatment of refractory partial-onset seizures.

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Introduction

There are three clinical types of partial seizures including simple partial, complex partial, and partial seizure evolving into secondarily generalized seizures. A task force of individuals from the American Academy of Neurology and the American Epilepsy Society provided evidence-based recommendations for the treatment of partial seizures [1,2]. In general, carbamazepine is considered first-line therapy for partial-onset seizures. However, less than 50% of patients will remain seizure-free after beginning initial antiepileptic drug (AED) therapy [3]. If carbamazepine fails to control the seizures, lamotrigine, topiramate, tiagabine, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and zonisamide may be either added to carbamazepine or used as monotherapy. Although these agents have demonstrated similar efficacy for the treatment of partial-onset seizures, they are not always well tolerated by patients. In fact, 20–30% of patients will discontinue therapy because of intolerable adverse drug effects (ADEs) [4]. Based upon the percentage of patients with epilepsy who are refractory to or unable to tolerate AEDs due to ADEs, it is evident that effective AEDs with minimal adverse drug reactions are needed. The manufacturers of lacosamide (other names include harkoseride, SPM-927, and ADD-234037) are hoping to assist in meeting this need. Lacosamide, unlike other AEDs, enhances the slow inactivation of voltage gated sodium channels (VGSCs) and interacts with the collapsin-response mediator protein-2 (CRMP-2) [5–7]. With

the addition of this novel mode of action, lacosamide may have a role as adjunctive treatment of partial-onset seizures with minimal ADEs. This review explores the role of lacosamide in the management of partial-onset seizures.

Lacosamide

Pharmacology

Lacosamide (R-2-acetamido-*N*-benzyl-3-methoxypropionamide) is a functionalized amino acid molecule believed to have a dual mode of action. It has been postulated that lacosamide selectively enhances the slow inactivation of VGSCs [5] and interacts with CRMP-2 [6]. Lacosamide shifts the slow inactivation curve to a more hyperpolarized potential, thereby selectively enhancing the slow inactivation of VGSCs. In return, this allows for more membrane potentials to enter the slow inactivation state prolonging depolarization. By prolonging depolarization, there are a limited number of neurons available for depolarization. This may ultimately lead to a decrease spread of a partial seizure. Unlike many other AEDs, lacosamide does not affect fast inactivation [5–7].

Lacosamide has been shown to interact with CRMP-2. It is not known what effect CRMP-2 has on seizure control. However, a study examining the hippocampus of patients with drug-resistant mesial temporal lobe epilepsy found reduced levels of CRMP-2 expressed compared to the control patients without epilepsy [8].

Lacosamide has been shown to interfere with CRMP-2 mediated neurotrophic effects, including axonal outgrowth [6]. Although the exact mechanism is not fully understood, this novel mechanism of interacting with CRMP-2 may be beneficial to patients with refractory seizures.

Pharmacokinetics

Lacosamide is rapidly and completely absorbed following oral administration displaying linear pharmacokinetics, with negligible first pass effect [9–11]. The bioavailability of lacosamide is approximately 100%, without regard to food. Intravenous (IV) lacosamide demonstrates bioequivalence when infused over 30 or 60 min [9,10].

Following oral administration, peak serum concentrations of lacosamide occur in approximately 1–4 h, with a plasma half-life of about 13 h [9–11]. Lacosamide is metabolized to its inactive metabolite, O-desmethyl metabolite, which has not been found to have any pharmacological activity. About 30% of the O-desmethyl metabolite and 40% of the unchanged lacosamide dose are renally eliminated.

Because lacosamide has minimal protein binding (<15%), the risk for drug–drug interactions is low. Although lacosamide was found to inhibit CYP-450-2C19 in *in vitro* studies at concentrations greater than 15 times higher than therapeutic plasma levels, no clinically relevant effects on plasma concentrations were found when lacosamide was given to poor or extensive metabolizers of CYP-2C19. Lacosamide has no effect on the serum levels of other AEDs, including carbamazepine, levetiracetam, lamotrigine, topiramate, valproate, zonisamide, gabapentin, and phenytoin. Other drug interaction studies have also found no effect on the pharmacokinetics of metformin, digoxin, oral contraceptives, and omeprazole [9–11].

Role in Epilepsy

Oral Lacosamide

Two open-label, multicenter studies were performed to investigate the safety and tolerability of lacosamide as adjunctive therapy in subjects with refractory partial seizures [12,13]. Eleven of the 13 subjects (84%) in the study by Fountain et al. were titrated to the maximal daily dose of 600 mg [12]. In the study by Sachdeo et al., 100 subjects were enrolled in the study, however data for analysis was only available for 90 subjects [13]. The median maximum tolerated dose was 300 mg/day with 40% of subjects having a maximum tolerated dose of 500 mg or 600 mg daily. It is unknown what other AEDs were used by the subjects in these two studies.

In a multicenter, double-blind, placebo-controlled trial, the safety and efficacy of lacosamide 400 mg daily, and 600 mg daily when added to concomitant AED therapy in 405 subjects with uncontrolled partial-onset seizures was evaluated [14]. During the baseline phase of the study, if subjects experienced at least eight seizures with no more than a 21-day seizure-free period, they were randomized in a 1:2:1 ratio to placebo, lacosamide 200 mg

twice daily or lacosamide 300 mg twice daily, respectively. Concomitant AEDs were held stable throughout the trial. The lacosamide dose was titrated by 100 mg daily increments per week to the randomized dose. The median percent reduction in seizure frequency (maintenance vs. baseline) per 28 days, using intent-to-treat analysis, was 20.8%, 37.3% ($P = 0.0078$), and 37.8% ($P = 0.0061$) for the placebo, 400 mg/day, and 600 mg/day groups, respectively. The 50% responder rates were 18.3%, 38.3%, and 41.2% for the placebo, 400 mg/day, and 600 mg/day groups, respectively. Only subjects completing the maintenance period with complete efficacy data were included in the seizure-free status analysis. The percentage of subjects that were seizure-free during the trial was 2.5% (400 mg daily) and 8.1% (600 mg daily). It is unknown what other AEDs were used by the subjects. The authors concluded that adjunctive lacosamide significantly reduced seizure frequency in patients with partial-onset seizures and was generally well tolerated.

In a multicenter, multinational, double-blind, placebo-controlled, randomized trial, the efficacy and safety of lacosamide 200, 400, and 600 mg daily in two equally divided doses when added to concomitant AED therapy in subjects with uncontrolled partial-onset seizures was evaluated [15]. During the baseline period, subjects must have had at least four partial seizures per 28 days on average, with no seizure-free period longer than 28 days. For subjects randomized to 600 mg daily, lacosamide was titrated in 100 mg daily increments each week for 6 weeks. Subjects randomized to 400 mg daily received placebo during the first 2 weeks of titration, then were started on lacosamide 100 mg daily at week 3 and the dose was increased by 100 mg daily increments each week until the randomized dose was reached. Subjects randomized to 200 mg daily received placebo during the first 4 weeks of titration, then were started on lacosamide 100 mg daily at week 5, with the dose being increased to 200 mg daily during week 6. Four hundred eighteen subjects were analyzed for safety and 415 subjects were included in the efficacy analysis. The median percent reduction in seizure frequency (maintenance vs. baseline) per 28 days, using intent-to-treat analysis, was 10%, 26%, 39% ($P = 0.023$), and 40% ($P = 0.0084$) for the placebo, 200 mg/day, 400 mg/day, and 600 mg/day groups, respectively. The 50% responder rates were 21.9%, 32.7% ($P = 0.899$), 41.1% ($P = 0.0038$), and 38.1% ($P = 0.0141$) for the placebo, 200 mg/day, 400 mg/day, and 600 mg/day groups, respectively. Seven subjects (1.7%) remained seizure-free during the trial. The dose that these subjects were receiving is unknown. It is also unknown what other AEDs were used by the subjects. The authors concluded that adjunctive lacosamide significantly reduced seizure frequency in patients with partial-onset seizures.

A multicenter, double-blind, placebo-controlled, randomized trial was performed to evaluate the efficacy and safety of lacosamide (200 and 400 mg daily) when added to one to three concomitant AEDs in 477 subjects with uncontrolled partial-onset seizures [16]. Subjects were to have had at least four partial seizures per 28 days on average, with no seizure-free period longer than 28 days during the period before enrollment as well as during the baseline period. For subjects randomized to 400 mg daily, lacosamide was titrated in 100 mg daily increments weekly. Subjects randomized to 200 mg daily received placebo during the first

2 weeks of titration, then were started on lacosamide 100 mg daily at week 3 and the dose was increased to 200 mg daily at week 4 of the titration period. The median percent reduction in seizure frequency (maintenance vs. baseline) per 28 days was 20.5%, 35.3% ($P = 0.02$), and 36.4% ($P = 0.03$) for the placebo, 200 mg/day, and 400 mg/day groups, respectively. The 50% responder rates were 25.8%, 35% ($P = 0.07$), and 40.5% ($P = 0.01$) for the placebo, 200 mg/day, and 400 mg/day groups, respectively. The percentage of subjects that were seizure-free during the trial was 2.1% (placebo), 3.6% (200 mg daily), and 2.4% (400 mg daily). It is unknown what other AEDs were used by the subjects. The authors concluded that adjunctive lacosamide significantly reduced seizure frequency in patients with partial-onset seizures and was generally well tolerated.

IV Lacosamide

A multicenter, double-blind, double-dummy, randomized trial was performed to evaluate the safety and tolerability of IV lacosamide as replacement therapy for oral lacosamide [17]. Subjects who were stable on twice daily dosing of oral lacosamide (200–600 mg daily) were randomized in a 2:1 ratio to one of two treatment groups: (1) IV lacosamide and placebo tablets twice daily or (2) IV placebo and oral lacosamide tablets twice daily. The first 30 subjects enrolled received the infusion over 60 min, to allow for safety data evaluation, before the next 30 subjects received a 30-min infusion. Subjects who received at least one dose of trial medication were included in the primary safety analysis.

Fifty-nine of the 60 subjects enrolled completed the trial. Eighty percent of subjects were seizure-free during the trial. The daily number of seizures experienced by subjects in this trial remained stable compared to baseline. The authors concluded that IV lacosamide, administered as 60- or 30-min twice daily infusions, showed a similar safety and tolerability profile to oral lacosamide for short-term replacement therapy. The percentage of subjects that had a 50% response rate was not reported.

A multicenter, open-label, inpatient trial was conducted to investigate whether IV lacosamide was safe and well tolerated when given twice daily as short-term adjunctive therapy in 160 subjects with partial seizures [18]. The investigators also attempted to identify appropriate infusion rate(s) for IV lacosamide. Subjects who were stable on twice daily dosing of oral lacosamide (200–800 mg daily) were placed into one of four cohorts: 30-min infusion ($n = 40$), 15-min infusion ($n = 41$), 10-min infusion ($n = 20$), and final 15-min infusion ($n = 59$). Subjects were given IV lacosamide twice daily for 2–5 days, per the discretion of the investigator and subject. Ninety-nine percent of subjects received at least 2 days of IV lacosamide twice daily and 53% of subjects in the 15-min and 10-min infusion groups received 3–5 days of therapy. The total daily dose received by subjects was 200–400 mg (61%), 500–600 mg (35%), or 700–800 mg (4%). Infusion site related adverse events were infrequently reported, vital signs remained stable, and seizure patterns for individual subjects did not change. The percentage of subjects that were seizure-free or had a 50% response rate were not reported. Seventy-two percent of subjects were treated with one or two concomitant AEDs, most commonly levetiracetam, carbamazepine, lamotrigine, or valproate.

Role in Status Epilepticus

One case report describing the successful use of lacosamide administered via percutaneous gastrostomy tube for the treatment of convulsive status epilepticus was published [19]. Temporary interruption of the seizures was achieved after administration of 150 mg (minced tablet powder) of lacosamide via gastrostomy tube. Complete clinical remission of the epileptic activity was achieved within 30 min of administration of a second 150 mg lacosamide dose (syrup) via gastrostomy tube. A second case report, describing the successful use of IV lacosamide for the treatment of non-convulsive status epilepticus, was published [20]. A 200-mg bolus was administered without dilution, and within 3–5 min, rhythmic epileptiform activity ceased. The patient recovered from her symptoms completely.

Lacosamide could be a treatment alternative if other, more established medications fail or are considered inappropriate. The authors of both case reports conclude that large, prospective studies are needed to assess the safety and efficacy of lacosamide in status epilepticus.

Adverse Effects

The adverse effects that occurred in at least 5% of subjects in at least one of the clinical trials discussed are summarized in Table 1 [14–18].

Data from the IV lacosamide open-label trials, suggest that lacosamide IV is overall well tolerated. Dizziness occurred in 5% and 6% of subjects receiving the IV lacosamide as 10- and 15-min infusions, respectively [18]. Dizziness, injection site pain, and somnolence was associated with the 30-min infusion, whereas headache, back pain, and dizziness was associated with the 60-min infusion [17,18]. Only minimal changes in the mean QTc interval and small increases in mean PR intervals were seen [17].

In a 6 month postmarketing experience, 52% (13/25) of patients reported side effects to lacosamide during the titration phase [21]. A sodium channel blocking anticonvulsant was used in addition to lacosamide in 70% of those patients reporting side effects. Most of the initial side effects did disappear during the

Table 1 Adverse effects associated with lacosamide [14–18]

Adverse effects	Subjects (%)
Abnormal coordination	5.3 to >10
Ataxia	13
Blurred vision	>10
Diplopia	9–12
Dizziness	6–35
Fatigue	5.6–14
Headache	7–16
Nausea	6.8–14
Nystagmus	6 to >10
Somnolence	>10
Tremor	>10
Upper respiratory tract infection	10
Vertigo	6.5
Vomiting	4.3–12

maintenance phase or with dose reduction. Two patients lost more than 10% of their body weight while receiving lacosamide, but they were also receiving other AEDs (zonisamide, lamotrigine, and levetiracetam). Three patients discontinued therapy as a result of intolerable side effects. The most common reported ADEs were fatigue, double vision, depression, dizziness, and nausea.

Contraindications/Precautions

There are no documented contraindications to lacosamide. Like other AEDs, lacosamide could potentially increase the risk of suicidal thoughts or behaviors [22]. In addition, lacosamide should be withdrawn over at least 1 week to decrease the potential of increase seizure frequency. Patients receiving lacosamide should be advised that it may cause dizziness and ataxia. Dizziness was one of the most commonly reported adverse effects and reason for discontinuation in clinical trials. Lacosamide should also be used in caution in patients with severe cardiac disease and patients who are receiving medications known to induce PR interval prolongation. It is recommended that patients with severe cardiac diseases obtain an ECG before beginning lacosamide and after titrated doses to steady state. Although no cases of atrial fibrillation or flutter were reported in epilepsy trials, studies in diabetic neuropathy revealed 0.5% of patients developed atrial fibrillation or flutter. Syncope was only reported in patients with diabetic neuropathy as well. Patients developing syncope were receiving doses greater than 400 mg/day of lacosamide. There is a risk for multiorgan hypersensitivity reactions when administering lacosamide. There has been one case of a patient developing symptomatic hepatitis and nephritis during initial clinical studies consistent with multiorgan hypersensitivity. Three other potential cases include two patients who developed a rash and elevated liver enzymes, and one patient who developed myocarditis and hepatitis.

Dosage and Administration

Lacosamide should be initiated at 50 mg twice daily for the adjunctive treatment of partial-onset seizures [22]. The dose can be increased weekly by 100 mg daily given as two divided doses, up to the recommended total daily dose of 200 or 400 mg. The Food and Drug Administration did not approve the 600 mg total daily dose, due to no additional benefit and the increased risk of additional side effects over a 400 mg total daily dose [22]. Patients receiving IV lacosamide can receive a dosage equivalent to their oral lacosamide dose. The IV dose should be infused over 30–60 min.

For patients with severe renal impairment, defined as a creatinine clearance of less than 30 mL/min, the maximum daily recommended dose is 300 mg [22]. A supplement dosage of up to 50% should be considered following a 4-h hemodialysis treatment. The maximum daily recommended dose for patients with mild or moderate hepatic impairment is 300 mg. It is recommended to exercise caution when increasing the dosage of lacosamide in patients with renal or hepatic impairment. Efficacy and safety of lacosamide in patients under 17 years old has not been established.

Lacosamide is available as 50 mg, 100 mg, 150 mg, and 200 mg tablets [22]. It is also available in a 200 mg/20 mL single dose vial,

which is stable at room temperature. The injection may be injected without further dilution and is compatible with sodium chloride injection 0.9%, lactated ringers, and dextrose.

Conclusions

Despite the limited number of placebo-controlled trials evaluating the safety and efficacy of lacosamide as adjunctive treatment for partial-onset seizures, the data suggests that lacosamide not only consistently reduces seizure frequency at doses ranging from 400 to 600 mg daily, but is also well tolerated. Lacosamide's pharmacokinetic profile minimizes the risk of drug interactions. These factors, in addition to its novel mechanism of action, make lacosamide an attractive alternative to other approved AEDs for the adjunctive treatment of partial-onset seizures.

Further research needs to be completed to define its role in status epilepticus refractory to other agents. Current literature supports the role of lacosamide adjunctive therapy for partial-onset seizures, however, the role of lacosamide as monotherapy needs to be established.

Lacosamide has also been studied for the treatment of diabetic neuropathic pain [23–31]. Although many studies in this area are promising, showing minimal improvement in clinical pain scores, additional randomized-controlled trials are necessary to determine its exact place in this condition.

Author Contributions

Both authors contributed equally to writing this review.

Conflict of Interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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