Lacosamide

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Summary: Lacosamide is a new chemical entity being investigated as an adjunctive treatment for epilepsy, as well as monotherapy for diabetic neuropathic pain. Lacosamide appears to have a dual mode of action: selective enhancement of sodium channel inactivation and modulation of collapsin response mediator protein-2. Rapidly and completely absorbed after oral administration, lacosamide has an elimination half-life of approximately 13 hours and a low potential for drug interactions. Additionally, lacosamide exhibits linear, dose-proportional pharmacokinetics with low intra- and interpatient variability. Randomized controlled trials of adjunctive lacosamide (200, 400, and 600 mg/day) have demonstrated statistically significant reduction in median seizure frequency compared with placebo. In addition, 50% responder rates for lacosamide (400 and 600 mg/day) were statistically superior to placebo. The most frequently reported adverse events (≥10% of lacosamide-treated patients) included dizziness, headache, and nausea. A double-blind, double-dummy randomized trial of intravenous lacosamide (30- and 60-minute infusion) as replacement for oral lacosamide showed that the safety and tolerability profiles were comparable for intravenous and oral lacosamide. The efficacy and safety results from completed clinical trials, as well as the favorable pharmacokinetic profile, suggest that lacosamide may represent a significant advance in antiepileptic drug therapy. **Key Words:** Lacosamide, antiepileptic drugs, anticonvulsants, epilepsy, partial-onset seizures.

INTRODUCTION

Lacosamide (*R*-2-acetamido-*N*-benzyl-3-methoxypropionamide; formerly harkoseride) is a member of a series of functionalized amino acid molecules that have been screened for anticonvulsant properties.[1–3] Studies have shown lacosamide to be an efficacious anticonvulsant in animal models.[4] Clinically, lacosamide is at present in a late stage of development as an adjunctive treatment for patients with uncontrolled partial-onset seizures, and has been assessed as monotherapy in patients with painful diabetic neuropathy. Results from completed trials suggest that an optimal lacosamide dose is in the range of 200 to 600 mg/day.

PHARMACOLOGY

Lacosamide demonstrated broad anticonvulsant effects in murine seizure models for generalized seizures, complex partial-onset seizures, and status epilepticus. In the maximal electroshock seizure (MES) test, lacosamide was more potent than phenytoin or phenobarbital.[2,3] It has also shown anticonvulsant activity in other *in vivo* seizure models, such as hippocampal kindling, audiogenic seizures, self-sustaining status epilepticus (SSSE), and amygdala kindling.[4–6] In SSSE rats, lacosamide reduced neuronal damage, indicating potential disease-modifying effects.[7]

Recent experimental studies indicate that lacosamide is likely to have a dual mode of action. Lacosamide appears to selectively enhance sodium channel slow inactivation, with no effects on fast inactivation.[8] In contrast, some antiepileptic drugs (AEDs), such as carbamazepine, phenytoin, and lamotrigine, affect the fast inactivation of voltage-gated sodium channels.[9] The enhancement of slow inactivation induced by lacosamide may help normalize activation thresholds and decrease pathophysiological neuronal activity, thus controlling neuronal hyperexcitability.

Lacosamide was protective in the psychomotor seizure (6 Hz) electroshock test with an ED_{50} of 9.99 mg/kg, unlike sodium-channel modulating AEDs, which are inactive or only slightly active in this model.[4] Additionally, modulation of collapsin response mediator protein-2 (CRMP-2) by lacosamide has been demonstrated in *in vitro* models.[10] Because CRMP-2 is part of the signal transduction cascade of neurotrophic factors and can

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convey neuroprotective effects,[11,12] this mechanism may contribute to the decreased neuronal loss observed in the SSSE model and the antiepileptogenic effects found in the electrical kindling model.[6]

Pharmacokinetics

Pharmacokinetic studies in healthy adults (≥18 years) indicate that orally administered lacosamide is rapidly and completely absorbed, with negligible first-pass metabolism. Lacosamide has a high oral bioavailability (approximately 100%) that is not affected by food.[3,13] Additionally, intravenous infusion of lacosamide at a dose of 200 mg with a duration rate of 30 or 60 minutes has demonstrated bioequivalence with the same dose of oral lacosamide.[14]

The pharmacokinetic profile of lacosamide exhibits low intra- and interpatient variability. After single-dose oral and intravenous administration, the plasma concentration of lacosamide increases proportionally with oral doses up to 800 mg and intravenous doses up to 300 mg.[3,7,15,16] After oral administration of lacosamide, peak plasma levels occur approximately 1 to 4 hours after the dose, and elimination half-life is approximately 13 hours.[3,17] A small proportion of lacosamide is demethylated to its primary metabolite, an *O*-desmethyl metabolite, which has demonstrated no pharmacological activity in *in vivo* models (T.S., unpublished observations, 2006). Lacosamide and its major metabolite are eliminated primarily by the kidney.

After single doses and at steady-state plasma concentrations, the pharmacokinetic profile of lacosamide shows a low age-related variability.[18] Furthermore, because lacosamide has minimal protein binding (<15%), the risk for displacement drug–drug interactions is low.[3,19] In drug interaction studies, lacosamide has shown no effect on the pharmacokinetics of carbamazepine, valproic acid,[19,20,21] metformin, digoxin, oral contraceptives (ethinyl estradiol/levonorgestrel),[21] or omeprazole (D.T., unpublished observations, 2006). Likewise, these drugs have shown no effect on the pharmacokinetics of lacosamide. In clinical studies, lacosamide has shown no influence on the plasma levels of concomitantly administered AEDs, including carbamazepine, levetiracetam, lamotrigine, topiramate, valproate, and phenytoin.[3,21,22] At present there is no indication that lacosamide acts as an inducer or inhibitor of the cytochrome P-450 (CYP-450) isoenzymes, except for the inhibition of CYP-2C19 *in vitro* at concentrations more than 15-fold higher than therapeutic plasma levels. Lacosamide plasma concentrations were comparable in poor and extensive metabolizers of CYP-2C19[21] and in individuals with inhibited CYP-2C19 (D.T., unpublished observations, 2006).

Therapeutic profile

Early trials. The initial patient trials of adjunctive lacosamide were multicenter, open-label evaluations of oral lacosamide in patients with partial-onset seizures. In the first trial, 13 patients received doses of lacosamide that were escalated from 200 to 600 mg/day in weekly increments of 200 mg/day.[23] In the third week of treatment, 11 of the patients achieved a maximum dose of lacosamide (600 mg/day). The most common adverse events reported by at least 10% of patients during this trial were dizziness, headache, ataxia, and nystagmus. Preliminary data showed a promising safety and seizure reduction profile, which supported the continued development of lacosamide.

In the next trial, the titration rate was decreased to 100 mg/day per week.[24] After a 4-week baseline period, the lacosamide dose was increased to the maximum tolerated dose (MTD), up to 600 mg/day, and then maintained for 4 weeks. A total of 91 patients taking one (21%) or two (79%) concomitant AEDs were exposed to lacosamide. The median MTD was 300 mg/day; approximately 50% of patients had an MTD of 400 to 600 mg/day. Among the 86 evaluable patients, 33% had at least a 50% reduction in seizure frequency, and 10% of patients were seizure-free throughout the 4-week maintenance period. The most common adverse events (≥10% of patients) included dizziness, diplopia, somnolence, fatigue, headache, accident not otherwise specified, ataxia, upper respiratory tract infection, vision abnormality, tremor, and nausea.

Placebo-controlled trials. Two large, multicenter, randomized, placebo-controlled trials of lacosamide as adjunctive therapy in patients with partial-onset seizures have been completed[25,26]; one trial is currently ongoing. These trials were designed to evaluate the efficacy and safety of lacosamide when administered concomitantly with up to three AEDs in patients with uncontrolled partial-onset seizures with or without secondary generalization. Randomized patients were required to have an average of at least four partial-onset seizures per 28 days, with no seizure-free periods lasting longer than 21 days during the 8-week baseline period. During the titration period of each trial, lacosamide was increased to the randomized dose in 100 mg/day weekly increments (50 mg twice daily). This titration period was followed by a 12-week maintenance period and an opportunity for transition to an open-label extension trial. In the two completed trials, 643 patients received lacosamide and 260 received placebo.

In the first randomized controlled trial,[25] 418 patients taking one (16%) or two (84%) concomitant AEDs were randomized (1:1:1:1) to placebo or target doses of lacosamide 200, 400, or 600 mg/day. During the 12-week maintenance period, patients in the lacosamide 400- and 600-mg/day dose groups showed statistically significant

reduction in median seizure frequency compared with placebo (400 mg/day: $p = 0.002$; 600 mg/day: $p = 0.008$). In addition, more patients from the lacosamide 400- and 600-mg/day dose groups experienced at least a 50% reduction in seizure frequency (400 mg/day: $p = 0.004$; 600 mg/day: $p = 0.014$) compared with placebo. Although reductions in seizure frequency were observed among patients in the lacosamide 200 mg/day dose group, these differences were not statistically significant. The most common adverse events in this trial (≥10% of lacosamide-treated patients) included dizziness, headache, nausea, fatigue, ataxia, vomiting, vision abnormality, somnolence, upper respiratory tract infection, and diplopia.

In the second randomized controlled trial, a similar design was used, but patients could take up to three concomitant AEDs.[26] A total of 485 patients were randomized (1:1:1) to either placebo or target doses of lacosamide 200 or 400 mg/day. Compared with patients in the placebo group, lacosamide-treated patients experienced a significantly greater reduction in median seizure frequency (200 mg/day: $p = 0.029$; 400 mg/day: $p = 0.016$) and a significantly larger number of patients experienced at least a 50% reduction in seizure frequency in the lacosamide 400-mg/day group ($p < 0.001$). The most commonly reported adverse events (≥10% of lacosamide-treated patients) during this trial were dizziness and headache.

An ongoing randomized controlled trial using a similar design has randomized 405 patients with uncontrolled partial-onset seizures to placebo or lacosamide 400 or 600 mg/day (1:2:1).

Open-label extension trials. After completing an open-label or placebo-controlled trial, patients were offered the opportunity to enroll in an open-label extension trial. To date, more than 90% of patients who completed a randomized controlled trial opted to continue oral lacosamide treatment (at doses of 100 to 800 mg/day) for up to 8 years in open-label extension trials. This participation will permit the evaluation of the long-term safety and tolerability of adjunctive lacosamide.

Intravenous lacosamide. To evaluate the safety and tolerability of intravenous lacosamide as replacement for oral lacosamide, 60 patients from an ongoing open-label lacosamide extension trial were enrolled in a multicenter, double-blind, double-dummy, randomized controlled trial.[27] Patients were randomly assigned (2:1) to receive either lacosamide solution for infusion (at a dose identical to their current oral dose) or intravenous placebo solution. Infusion duration was either 60 or 30 min. To maintain the blind, the two patient groups also received placebo tablets or oral lacosamide tablets, respectively. All patients but one received four intravenous infusions of lacosamide over 2 days. Three patients receiving intravenous lacosamide reported dizziness, and two patients reported injection site pain. In this trial, lacosamide solution for intravenous infusion was successfully used as short-term replacement for oral lacosamide in patients with partial-onset seizures. The pharmacokinetics and bioavailability of intravenous lacosamide after 60- and 30-minute infusions were comparable to those of oral lacosamide at the same dose.

A multicenter, open-label, inpatient trial to evaluate the safety and tolerability of intravenous lacosamide at doses ranging from 200 to 800 mg/day, with twice-daily infusion durations of 10, 15, or 30 minutes, has enrolled 160 patients and is currently ongoing.

Overall safety and tolerability. In completed randomized controlled trials, the most frequently reported adverse events (≥10% of lacosamide-treated patients) were dizziness, headache, and nausea. The events that most often led to trial discontinuation were dizziness and nausea. There were no significant differences in the rate of psychiatric adverse events or in individual psychiatric adverse events between patients receiving lacosamide or placebo. Overall, the rates of psychiatric adverse events were 4% or less for any individual adverse event in any treatment group.

Chronic administration of lacosamide showed little effect on the plasma concentrations of concomitant AEDs. Lacosamide generally had no clinically important effects on laboratory, vital sign, or body weight variables. Lacosamide produced a small, dose-related increase in mean PR interval on the electrocardiogram (4.2 to 4.6 ms for the 400-mg/day dose).

In the one completed and three ongoing long-term extension trials in patients with partial-onset seizures, the general safety profile of oral lacosamide to date is similar to that seen in shorter-term trials with lacosamide as well as other newer AEDs.[28] A comprehensive evaluation of the safety profile of lacosamide (including the frequency of cardiovascular and other adverse events) will be completed once ongoing trials are concluded.

The safety and tolerability profile of intravenous lacosamide appeared to be similar to that of oral lacosamide.

CONCLUSIONS

Pharmacological therapy for patients with uncontrolled partial-onset seizures is often difficult and can be complicated by drug–drug interactions. Lacosamide is an investigational AED in development for the treatment of partial-onset seizures, which has properties that may be useful for a broad range of patients.

Lacosamide possibly offers a dual mode of action with potential disease-modifying effects via CRMP-2 modulation. Neuroprotective effects have been shown in several preclinical studies, and further studies are planned to explore the neuroprotective potential of the compound. The effect of lacosamide on sodium channels is different

from that of other sodium channel-modulating drugs. Lacosamide selectively enhances sodium channel slow inactivation with no effects on fast inactivation, whereas other sodium channel-modulating drugs show no effect of enhancing sodium channel slow inactivation.

In clinical trials to date, lacosamide at doses of 200 to 600 mg/day significantly improved seizure control in patients with uncontrolled partial-onset seizures taking up to three concomitant marketed AEDs. The adverse event profile of lacosamide is similar across trials, and lacosamide is associated with a low rate of psychiatric adverse events. Lacosamide provides high oral bioavailability unaffected by food, good tolerability with twice-daily dosing, and minimal drug–drug interactions. For patients who are temporarily unable to take oral lacosamide, the equivalent safety and efficacy of intravenous lacosamide may provide an added benefit.

The efficacy and safety results obtained in completed clinical trials combined with the favorable pharmacokinetic profile of lacosamide suggest that lacosamide may be a significant advance in AED therapy.

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