Lacosamide, a newer antiepileptic

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ABSTRACT

Lacosamide (LCM) is a newer antiepileptic drug with a dual mode of action. It selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation, and modulates collapsing response mediator protein 2 (CRMP-2). It has a high oral bioavailability of approximately 100%. It has shown potent and broad neuroprotective effects in vitro and in vivo animal models making it a potential candidate for long term treatment of epilepsy. In addition to this, it has demonstrated analgesic activity in various animal models. Apart from this, LCM has demonstrated potent effects in animal models for a variety of CNS disorders like schizophrenia and stress induced anxiety. Various safety pharmacology and toxicology studies have shown that LCM is well tolerated. Clinical trials have also suggested that LCM is a safe, effective, and well tolerated adjunctive treatment for reduction of seizure frequency in patients with highly refractory, partial seizures. Other potential indications of LCM are being investigated.

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In the last decade, 10 new drugs offering appreciable advantages in terms of their favorable pharmacokinetics, improved tolerability, and lower potential for drug interactions were introduced to the antiepileptic drug (AED) armamentarium. However, despite the large therapeutic range of old and new AEDs, approximately 30% of the patients with epilepsy are still not seizure free. Thus, there is a substantial need to develop new AEDs. Challenges involved in the development of novel treatment strategies for epilepsy include broader clinical efficacy, improved tolerability, least toxicity, favorable pharmacokinetics, and lower potential for drug interactions. Lacosamide (LCM), a recently developed novel antiepileptic drug as suggested by preclinical data meets all the aforementioned criteria. Lacosamide, (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is a functionalized amino acid, which has shown analgesic and anticonvulsant effects in a large variety of animal models. Various pharmacokinetic studies have reported complete absorption after oral administration. In vitro results showed no or low potential to inhibit or to induce cytochrome P-450 (CYP-450) isoforms, thus indicating its low potential for drug-drug interactions. It has demonstrated neuroprotective effects in vitro and in vivo animal models. Furthermore, it has also been shown to be effective in schizophrenia and stress induced anxiety. Currently, LCM is in phase III clinical development for adjunctive treatment for patients with uncontrolled partial onset seizures and for treatment of painful diabetic neuropathy. Safety studies involving the central nervous, respiratory, gastrointestinal, and renal systems have reported none or only minor side effects without any indication of abuse liability. The present review provides an overview of LCM.

Chemistry. Chemically, LCM is (R)-2-acetamido-N-benzyl-3-methoxypropionamide (Figure 1). It belongs to the class of functionalized amino acids. It is a white to yellow crystalline powder with a molecular weight of 250.30 Da. Its molecular formula is $C_{18}H_{18}N_2O_3$.

Pharmacology. Mechanism of action. Based on recent experimental studies, a novel, dual mode of action has been suggested for LCM-enhancement of sodium channel slow inactivation and modulation of collapsing response mediator protein 2 (CRMP-2).
Both are novel mechanisms for an AED. It is suggested that LCM selectively enhances sodium channel slow inactivation, without affecting fast inactivation, which helps in normalizing activation thresholds and decreasing pathophysiological neuronal activity, thus controlling neuronal hyperexcitability. The CRMP-2 is a part of the signal transduction cascade of neurotrophic factors and can convey neuroprotective effects. Thus, the ability of LCM to modulate CRMP-2 contributes to the decreased neuronal loss observed in status epilepticus animal models and its potential anti epileptogenic effects as seen in animal models.

**Pharmacokinetics.** Pharmacokinetic studies have reported rapid and complete absorption of LCM from the gastrointestinal tract after oral administration. It has a high oral bioavailability of approximately 100%. Administration with food does not alter the rate and extent of absorption. An elimination half-life of 13 hours allows twice daily dosing. Lacosamide is not substantially metabolized in vitro, 95% of the dose is excreted in the urine, around 40% as unchanged drug, and 30% as main but inactive O-desmethyl. In vitro results have shown no or low potential to inhibit or to induce CYP isoforms 1A2, 2A6, 2C9, 2D6, 2E1, and 3A4 except CYP2C19. Lacosamide has shown no influence on plasma levels of the AEDs studied in patients with partial seizures with or without secondary generalization. In healthy volunteers, LCM has shown no effect the plasma concentration of the cytochrome P-450 (CYP-450) enzyme inducer carbamazepine (CBZ), or the CYP-450 enzyme inhibitor valproic acid; moreover, the plasma concentrations of LCM were not affected by CBZ or valproic acid. Since LCM has low protein binding, drug displacement interactions are unlikely. Pharmacokinetic studies of LCM have shown a linear relationship for oral doses ranging from 100-800 mg/day.

**Preclinical studies for various indications. Anticonvulsant activity.** Preclinical studies have demonstrated that LCM protects against seizures in various anticonvulsant animal models. As compared to the commonly used anti-epileptics, LCM has shown a unique profile in animal models for epilepsy.

**Neuropathic pain.** Furthermore, LCM has demonstrated antinociceptive potential in experimental animal models that reflect distinct types and symptoms of pain. It has shown anti hyperalgesic effects in different models for acute and chronic inflammatory pain with similar or even higher potency and efficacy as compared to other anticonvulsant drugs, thus making it a potential drug for the treatment of pain conditions such as arthritis. Lacosamide has exhibited potent and broad-spectrum antinociceptive efficacy on a streptozotocin rat model of diabetic neuropathic pain in comparison with drugs that are commonly used in the treatment of diabetic neuropathic pain, that is, antidepressants and anticonvulsants.

**Neuroprotection.** In vitro studies have shown the potent anti-apoptotic effects of LCM. Lacosamide attenuated brain damage in ischemic animal models. Its potent and broad neuroprotective effects in vitro and in vivo animal models make it relevant for long term treatment of epilepsy.

**CNS disorders.** Therapeutic efficacy for various CNS disorders has been reported recently. Lacosamide has shown anti tremor efficacy higher than reference compounds primidone and propranolol in a harmaline rat model for essential tremor. It was reported that LCM acts synergistically with clozapine to enhance prepulse inhibition of the acoustic startle reflex in mice (an animal model for schizophrenia) and has anti-dyskinetic effects in animal models for tardive dyskinesias. These preclinical findings suggest LCM as a suitable add-on drug for schizophrenia. In addition to this, LCM reportedly attenuates stress-induced hyperthermia suggesting potential activity in stress related mood disorders, for example, post-traumatic stress disorder.

**Clinical trials. Epilepsy.** Three randomized, placebo-controlled clinical trials with a 12-week maintenance period with LCM (at doses of 200 mg, 400 mg, or 600 mg per day) have been carried out. All the trials used very similar designs and involved 1,308 patients with a history of an average of 23 years of partial-onset seizures. The purpose of these trials was to evaluate the efficacy and safety of LCM when administered concomitantly with 1-3 AEDs in adults with uncontrolled partial-onset seizures with or without secondary generalization. The first trial involved 485 patients taking up to 2 concomitant AEDs and randomized to placebo or LCM 200 mg or 400 mg, the 50% responder rate was significantly significant for LCM 400 mg (41%) than for placebo (26%). In another trial, 418 patients taking one or 2 concomitant AEDs were randomized to
placebo or LCM 200 mg, 400 mg, or 600 mg following an 8-week baseline period. The drug was titrated in weekly increments of 100 mg per day over 6 weeks and maintained for 12 weeks. The responder rate, defined as a reduction of at least 50% in seizure frequency from baseline to maintenance, was significant over placebo (for which the responder rate was 22%) for LCM 400 mg (41%), and LCM 600 mg (38%). In the third trial,9 conducted in 405 patients taking up to 3 concomitant AEDs, 50% responder rates on both dosages tested (400 mg and 600 mg) were significantly superior to placebo (38% and 41% versus 18%). Data from these trials suggest that the proportion of patients with a 50% reduction in seizure frequency was 23% for placebo, 34% for LCM 200 mg per day, and 40% for LCM 400 mg per day. A statistically significant reduction in 28-day seizure frequency (baseline to maintenance phase) as compared with the placebo group was observed with LCM 200 mg per day in the second trial, 400 mg per day in all 3 studies, and 600 mg per day in both studies with this dose. Although the efficacy of LCM 600 mg per day was similar to LCM 400 mg per day, yet patients were less likely to tolerate this dose because of CNS- and gastrointestinal-related adverse effects, and the maximum recommended dose is 400 mg per day.27-9

Neuropathic pain. In a smaller open-label follow-on trial of people with diabetic neuropathy,10 LCM also provided significantly better pain relief as compared to placebo. This trial was designed to investigate long-term safety and efficacy of LCM in patients with painful diabetic neuropathy. After one-week baseline period, LCM 100 mg/day was started with a 20-week maintenance period. Thereafter, patients could opt to continue LCM up to around 2.5 years (extension period). The doses were escalated by 100 mg/day to an optimal level, up to a maximum of 400 mg/day every week, based on pain and safety assessments. The trial involved 69 patients with painful diabetic neuropathy. Of the 69 enrolled patients, 47 (68%) completed the 20-week maintenance period and elected to continue into the extension period; 37/69 (54%) patients were in the extension period for more than one year and 34/69 (49%) continued until study termination. The modal LCM dose in most patients (54%) was 400 mg/day. The most frequently reported adverse events (10% of patients) were headache, upper respiratory tract infection, arthralgia, sinusitis, nasopharyngitis, and back pain. Significant reductions from baseline in Likert pain scores began during dose titration and were sustained throughout the study. Neuropathic Pain Scale, Quality of Life scores, and Patient’s Global Impression of Change assessment also demonstrated significant improvements. Out of 34 patients at study termination, 32 (90%) elected to continue with LCM treatment in another long-term open-label trial. Data from this analysis support the long-term safety profile and sustained efficacy of LCM for treatment of painful diabetic neuropathy.10

Safety pharmacology and toxicological studies. Safety pharmacology and toxicology studies conducted in mice, rats, rabbits, and dogs have shown that LCM is well tolerated. Delay in cardiac conduction due to inhibition of cardiac sodium current is an adverse effect shared with other anticonvulsant drugs acting on the sodium channel like CBZ or phenytoin.11 Cardiovascular side effects were observed in anesthetized dogs, the most sensitive animal species tested, starting at plasma levels, which are similar to these obtained after 600 mg of LCM in clinic. However, the same plasma levels were measured at the no-observed-adverse-effect level (NOAEL) in awake dogs in a one-year toxicological study. Otherwise, either none or only minor side effects were observed in safety studies involving the central nervous, respiratory, gastrointestinal, and renal systems, and there is no indication of abuse liability. No genotoxic or carcinogenic effects were observed in vivo. Its preclinical safety profile has been evaluated at all stages of reproduction, namely, effects on fertility, early, and embryo-fetal development and pre/postnatal development including maternal function. It had no effect on fertility and reproductive function of male or female rats. Though no teratogenic properties in rats or rabbits were seen, developmental toxicity was observed at a maternally toxic dose. Furthermore, it was tested for developmental toxicity in juvenile rats showing no age specific toxicity except for a slight delay in overall development at the highest dose.11

Present status. Currently, LCM has been approved by the European Commission as an adjunctive therapy for partial-onset seizures with or without secondary generalization in patients with epilepsy aged 16 years and older. Lacosamide is approved by the FDA as an adjunctive therapy for partial-onset seizures in patients with epilepsy aged 17 years and older,8 and it is being assessed as monotherapy in patients with painful diabetic neuropathy.

Future prospects. Lacosamide is under evaluation for osteoarthritis, cancer pain, central pain, and fibromyalgia. Further trials to identify LCM’s potential in pain and for other indications have been initiated.

In conclusion, LCM has demonstrated a promising preclinical profile in terms of mechanism of action, spectrum of activity, pharmacokinetics, and safety profile, which is quite different from other anticonvulsants. Data from clinical trials have supported LCM as a safe, effective and well tolerated adjunctive treatment for subjects with highly refractory, partial seizures. It has
also shown efficacy in the treatment of painful diabetic neuropathy. Thus, LCM represents a first-in class promising new drug candidate with a broad spectrum of action including epilepsy, diabetic neuropathic pain, and other indications.

Acknowledgment. We would like to thank Dr. P. K. Singh, Dr. Prasad Byrav D. S. and Mr. Ajay Prakash for their valuable contribution while writing the manuscript.

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