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Review article

Lacosamide as monotherapy in focal seizure: Literature review

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ABSTRACT

Lacosamide is a newer approved antiepileptic drug (AED) characterized by its novel pharmacodynamic profile. It is now approved by United States Food and Drug Administration for use as monotherapy in adults (aged >17 years) with focal seizures based on historical controlled trial by Wechsler RT et al in 2014. Randomized controlled trials on lacosamide monotherapy have demonstrated significant reduction in median seizure frequency. In addition, 50% responder rates for lacosamide was noted in half of the patients, with retention rate in two third of patients in 1 year follow up period. Adverse events reported in clinical trials were mostly mild to moderate in intensity. The most common adverse events were dizziness, headache, convulsion, nausea and fatigue while convulsion and dizziness were commonly responsible for drug discontinuation. Overall, lacosamide monotherapy can be a good treatment option in patients with focal seizure.

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1. Introduction

Epilepsy is a brain disorder defined by at least two unprovoked (or reflex) seizures occurring >24 h apart and one unprovoked seizure and a probability of further seizures in next 10 years. Epilepsy is clinically presented as recurrent seizures due to abnormal synchronous or excessive neuronal discharge in the brain.[1] Seizures are classified as generalized seizures (synchronized discharges involving both hemispheres), or focal seizures (previously called partial-onset seizures) involving one cerebral hemisphere.[2] The worldwide prevalence of epilepsy is between 4 and 10 per 1000 population,[3] while in India it is 5.59 per 1000 population with equally distributed between men and women or urban and rural region.[4]

The goal of pharmacotherapy with antiepileptic drugs (AEDs) is to reduce the frequency of epileptic seizures and achieve a seizure-free state.[5] There are evidences that the majority of seizure patients can achieve seizure freedom with monotherapy, but only four AEDs i.e. felbamate, lamotrigine, oxcarbazepine, and topiramate are being approved by United States Food and Drug Administration (USFDA) as monotherapy, and only topiramate and oxcarbazepine have an indication for initial monotherapy.[6–9] Another 4 drugs have been considered as conversion to monotherapy in U.S.: lamotrigine extended-release, levetiracetam extended-release, pregabalin and eslicarbazepine.[10–13]

Lacosamide (R-enantiomer of 2-acetamido-*N*-benzyl-3-methoxypropionamide, previously known as harkoseride or ADD 234037) is a newer approved AED characterized by his novel pharmacodynamic profile.[14] Lacosamide (LCM) was approved in 2008 by the European Medicines Agency (EMEA)[15] and by the US

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FDA[16] as adjunctive treatment in patient aged >16 years (EMEA) and 17 years (FDA) with focal seizures with or without generalization and is newly licensed in 2014 by US FDA[16] for use as monotherapy in adults (aged >17 years) with focal seizures. Oral lacosamide is available in 50, 100, 150 and 200-mg in tablet form and 10 mg/ml in oral solution. An intravenous formulation (10 mg/ml) is also available for short-term replacement of oral LCM but it is not currently approved for status epilepticus (SE).[16]

This article reviews the therapeutic use of lacosamide as monotherapy in patients with focal seizures along with an overview of its novel pharmacological properties.

2. Pharmacodynamic properties

The specific mechanism by which LCM exerts its antiepileptic effects in humans is not yet known.[16] Recent study results suggest that LCM has a dual mode of action responsible for its anticonvulsant and analgesic activity.[14] LCM has an effect on the voltage-gated sodium channels (VGSCs). LCM has unique ability to with the slow inactivation of VGSCs with no role in fast inactivation, unlike other AEDs, such as carbamazepine, phenytoin and lamotrigine inhibit both slow and fast inactivation of VGSCs.[17] This enhancement of slow inactivation of sodium channels controls neuronal hyperexcitability by normalizing activation thresholds and decreasing pathophysiological neuronal activity.[18]

Lacosamide also exerts its action by binding to collapsing-response mediator protein-2 (CRMP2), a phosphoprotein that is involved in neuronal differentiation and control of axonal growth.[19,20] However, this binding has recently been debated as in vitro study has advocated that LCM does not specifically bind to CRMP-2.[21]

3. Pharmacokinetic properties

Following oral administration, LCM is rapidly and completely absorbed after single dose with negligible first pass effect with absolute bioavailability ~100%. Maximum LCM serum concentration is attained in 1–4 hours after oral administration and immediately after intravenous infusion. There is no effect of food on the rate and extent of absorption. Steady-state plasma levels (C_{ss}) are achieved after 3 days of twice daily oral administration. The plasma concentration of LCM shows linear and proportional increase with increasing oral and intravenous doses up to 800 and 300 mg, respectively, with low inter- and intra-subject variability. Intravenous infusion of LCM 200 mg is bioequivalent to the same dose administered orally in healthy volunteers. A single oral dose of 200 mg approximates steady-state concentrations which is comparable to the oral dose of 100 mg twice a day.[16,20,22,23]

Lacosamide exhibits negligible plasma protein binding (<15%) and has a volume of distribution (~0.6L/kg) equal to total body water. LCM is mainly excreted from the systemic circulation by kidney and biotransformation. After oral and intravenous administration, approximately 95% of radioactivity administered is excreted in the urine mainly as unchanged lacosamide (~40% of the dose), its O-desmethyl metabolite (~30%), and ~20% as a structurally unknown polar fraction and small amount (< 0.5%) in the feces. CYP3A4, CYP2C9, and CYP2C19 isoforms are mainly involved in the metabolism of O-desmethyl metabolite. The elimination half-life of the unchanged lacosamide is ~13 h and its *O*-desmethyl metabolite is 15–23 hours. Elimination is not altered by any type of dosing, multiple dosing or intravenous administration.[16,20,22,23]

Lacosamide has shown no pharmacokinetic differences in special population like age (>65 years), gender, race or CYP2C19 polymorphism.[16] There is no clinically significant drug-drug interaction of lacosamide with commonly used AEDs like valproic acid, carbamazepine, gabapentin, levetiracetam, phenytoin) and drugs that undergo CYP-mediated biotransformation like warfarin, midazolam, omeprazole (Table 1).[22]

4. Efficacy of Lacosamide as monotherapy

Lacosamide has been approved for monotherapy by the US FDA based on historical controlled trial by Wechsler RT et al.[24] in 2014 and its efficacy as monotherapy has been established in prospective,[25] retrospective study[26] each and data presented in abstract format at the conference.[27–29]

The efficacy of conversion from stable dosages of 1–2 AEDs to oral lacosamide monotherapy was evaluated in patients (age 16-70 years) in a historical-cohort controlled, double-blind study [ALEX-MT] (A Lacosamide EXchange to Monotherapy Trial) conducted by Wechsler et al.[24]. Those patients experiencing 2–40 focal seizures per 28 days during the 8-week prospective baseline were eligible for randomization to lacosamide 400 (n = 319) or 300 mg/day in 3:1 proportion. A 300 mg/day treatment group (n = 106) was included to blind treatment group (400 mg/day). Study was conducted in two phases: 3 week titration phase and 16 week lacosamide maintenance phase (6 week withdrawal phase in which background AEDs has been withdrawn and 10 week monotherapy phase). The primary efficacy outcome was the percentage of patients receiving lacosamide 400 mg/day who met ≥ 1of the exit criteria (Table 2) by day 112 of the maintenance phase in the full analysis set (n = 284; i.e. patients who completed the titration phase and initiated withdrawal phase) compared with the prespecified historical-control exit percentage (65.3%). Analyses were done by using Kaplan–Meier estimates.

By day 112, the percentage of patients in the lacosamide 400 mg/day monotherapy group meeting at least one exit criterion was 30.0% (95% CI 24.6–35.5%) which was superior than historical control, as the upper limit of the 95% confidence interval was lower than the historical-control exit percentage (35.5% versus 65.3%). The mean time to exit due to meeting at least one exit criterion during maintenance phase was 45.0 days in the lacosamide 400 mg/day monotherapy group. Median duration of lacosamide monotherapy 400 mg/day treatment was 71 days during maintenance phase. In addition, Patient's Global Impression of Change

Table 1
Main characteristics and pharmacokinetic properties of lacosamide.[20]

Absolute bioavailability	100%
T_{max}	1–4 h
C_{max}	8.7 ± 1.8 μg/ml
Elimination $t_{1/2}$	13 h
Plasma protein binding	15%
Volume of distribution	0.6 L/kg
Effect of food on absorption	No
Route of elimination	Renal
Significant drug interaction with other antiepileptic drugs or with warfarin, midazolam, metformin, omeprazole, digoxin, estrogen	No
Dose conversion from oral to intravenous or vice versa	No

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