Review Article

A Review on New Antiepileptic Drug – Lacosamide and its Analytical Methods

R. Valarmathi*, S. Farisha Banu, S. Akilandeswari, R. Senthamarai and CS. Dhivya Dhharshini

*Department of Pharmaceutical Analysis, Periyar College of Pharmaceutical Sciences, Trichy, Tamil Nadu, India.

ABSTRACT

Epilepsy is the most common neurological disorder results in excessive electrical activity in part or all of the brain resulting in recurrent seizures. Lacosamide (LCM) is a new antiepileptic drug approved by US-FDA for the treatment of partial onset seizures. It acts in a new way that it has two novel mechanisms of action which differs from other existing anti epileptic drugs. Lacosamide has less severe side effects and less drug interactions with other drugs. There are several analytical methods including UV, HPLC, HPTLC have been reported for determination of lacosamide in bulk and its pharmaceutical dosage forms. Lacosamide in human and rat plasma is determined using LC-MS. Stability indicating HPLC have also been reported for Lacosamide.

Keywords: Lacosamide, partial onset seizures, UV, HPLC, HPTLC, LC-MS.

INTRODUCTION

Epilepsy[1] is a disorder of brain's electrical system where a person has seizures over time. Seizures are episodes of distrurbed brain activity that cause changes in movement, behaviour, sensation and awareness. Epilepsy is one of the most common neurological disorders affecting upto 2% of the population worldwide. According to the Indian Epilesy Association[2], around 10% of the population in India suffers from Epilepsy. About 30% of the epileptic patients treated with available antiepileptic drugs (AEDs) continue to have seizures and are considered therapy-resistant or refractory patients.

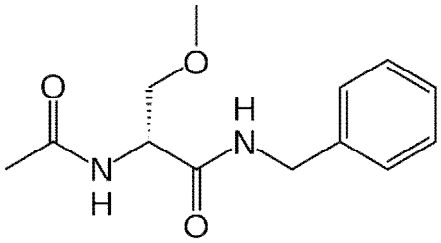
Among different types of epileptic seizures, partial onset seizure tops second most among the population[3]. Despite the advent of new antiepileptic drugs(AEDs) over the past 15 years, the treatment of uncontrolled partial-onset seizures remains a dilemma for clinicians. Currently available AEDs have significant drug interactions and adverse drug reactions. So there is a need for a new antiepileptic drugs with minimal drug interaction and less severe side effects.The most recent AEDs offer new mechanisms of action and favourable pharmacokinetic and safety profiles.

Lacosamide is the latest AED approved by US- FDA for adjunctive use in partial-onset seizures in patients 17 years of age and older[4]. It differs from all other approved AEDs in that it has two novel mechanisms of action and favourable pharmacokinetic and safety profiles. The potential for drug interactions with other AEDs and currently prescribed medications is very low. Overall there is a minimal dosing and clinical monitoring requirement with Lacosamide.

CHEMISTRY [4,5]

Lacosamide is ®-2-acetamido-N-benzyl-3-methoxypropionamide. Lacosamide is a member of functionalized aminoacids. It occurs as a white to slight yellow crystalline powder with a molecular weight of 250.294 g/mol.

Drug Profile [6,7]

Structure	
Chemical name	®-2-acetamido-N-benzyl-3-methoxypropionamide
Molecular weight	250.294 g/mol
Molecular formula	$C_{13}H_{18}N_2O_3$
Melting point	140-146° C
Storage conditions	20-25° C
Dosage forms available	tablets, syrup and injections

SOLUBILITY[7]

It is soluble in organic solvents such as ethanol, DMSO and dimethyl formamide, slightly soluble in acetonitrile, soluble in phosphate buffered saline at pH 7.2.

PHARMACOKINETICS[9]

Lacosamide undergoes minimal first-pass metabolism and is eliminated by renal excretion (40%) and biotransformation. Lacosamide has a half-life of 13 hours, displays a first-order pharmacokinetic elimination profile and is administered twice. Protein-binding is minimal (less than 15%) and plasma concentrations are consequently linear and proportional for doses up to 800 mg per day and steady state is achieved at 3 days.

MECHANISM OF ACTION[10-14]

Lacosamide works completely in a new way and has dual novel mechanisms of action.

- It selectively enhances slow inactivation of voltage gated sodium channels, stabilizing hyperexcitable neuronal membranes and inhibiting neuronal firing.Its inhibitory actions are distinct from thosewith AEDs that act via fast inactivation of sodium channels. Other physiological activities remains undisturbed due to slow inactivation
- Lacosamide modulates collapsin response mediator protein-2(CRMP-2). The role of CRMP-2 has not been fully elucidated, however, its expression is altered in epilepsy and other neurodegenarative diseases

DRUG INTERACTIONS[15]

Lacosamide displays a favorable interaction profile with currently prescribed AEDs and other commonly used medications. No food–drug or drug–drug interactions with other marketed agents (i.e., digoxin, metformin, omeprazole, and oral contraceptives containing ethinylestradiol and levonorgestrel) that could be affected by the CYP2C19 pathway or protein binding at therapeutic levels have been identified.

SIDE EFFECTS [16-17]

- dizziness, spinning sensation
- loss of balance or coordination
- blurred vision
- nausea, vomiting
- drowsiness, tired feeling
- headache
- double vision

VARIOUS ANALYTICAL METHODS FOR LACOSAMIDE

Ultraviolet Spectroscopy[18,19]

Lacosamide has been analysed by UV spectroscopy using water as solvent at 257nm. Beer's law was found to be obeyed in the concentration range of 300-900µg/mL. Another simple method using

acetonitrile and water as solvent has been performed at a wavelength 230 nm and this method was found to be linear at concentration ranging from 12-40µg/mL.

HPLC using UV detector[20,21]

This method has been developed for Lacosamide, in its pure form as well as in tablet dosage form. Chromatography was carried out on a Symmetry C18 (4.6 x 150mm, 5 µm) column using a mixture of Methanol and phosphate buffer (65:35 v/v) as the mobile phase at a flow rate of 0.7 mL/min, the detection was carried out at 215nm. The retention time of the drug was 2.56±0.02 min. The method produced linear responses in the concentration range of 10-60 mg/ml of Lacosamide. The method precision for the determination of assay was below 2.0%RSD.

Another isocratic reverse phase liquid chromatography (RP-LC) method has been developed for the determination of Lacosamide in Bulk and its pharmaceutical formulation. Separation was achieved with a Develosil ODS HG-5 (150 mmx4.6 mm I.D; particle size 5 µm) Column and Sodium di-hydrogen phosphate monohydrate buffer (pH adjusted to 3.0 with diluted orthophosphoric acid): Acetonitrile (700:300) v/v as eluent at flow rate 1.0 mL/min and the Column temperature was 40°C. UV detection was performed at 210nm and sample temperature was maintained at 5°C. The method is linear over a range of 3.996 µg/mL to 47.952 µg/mL.

Stability indicating HPLC Method [22,23]

A novel stability-indicating reverse phase high pressure liquid chromatographic assay method was developed and validated for the determination of lacosamide (LCM). This method was developed based on forced degradation data obtained by HPLC analysis. Lacosamide was subjected to stress under the conditions of hydrolysis (acidic, basic and neutral), oxidation, thermal and photolysis. The separation of degradation products from lacosamide was accomplished on Hypersil BDS C18 Column using (250 x 4.6mm, 5µm) 0.01M mono basic potassium phosphate for adjusting the pH to 4.0 with orthophosphoric acid: acetonitrile (30:70, v/v) as mobile phase. The flow rate was 1.0 mL/min and the detection was carried out at 215 nm.

An isocratic stability indicating reversed-phase liquid chromatographic determination was developed for the quantitative determination of lacosamide in the pharmaceutical dosage form. A Hypersil C-18, 4.5 µm column with mobile phase containing acetonitrile-water (20:80, v/v) was used. The flow rate was 1.0 mL min-1 and effluents were monitored at 258 nm. The retention time of lacosamide was 8.9 min. The method was found to be linear in the concentration range of 5-100 µg/ml and the recovery was found to be in the range of 99.15- –100.09%. The limit of detection and limit of quantification were found to be 2 and 5 µg/ml, respectively. Lacosamide stock solutions were subjected to acid and alkali hydrolysis, chemical oxidation and dry heat degradation. The drug was found to be stable to the dry heat and acidic condition attempted.

HPLC using Tandem Mass Spectrometry [24]

A rapid, simple and sensitive liquid chromatography–tandem mass spectrometry (LC/MS/MS) was developed for the determination of an antiepileptic drug, lacosamide, in rat plasma. The method involves the addition of acetonitrile and internal standard solution to plasma samples, followed by centrifugation.. The separations were performed on column packed with octadecylsilica (5µm, 2.0×50mm) with 0.1% formic acid and acetonitrile as mobile phase, and the detection was performed on tandem mass spectrometry by the multiple-reaction monitoring via an electro spray ionization source. The standard curve was linear over the concentration range from 0.3 to 1000ng/mL. The lower limit of quantification was 0.3ng/mL using 50µL of rat plasma sample. The intra- and inter-assay precision and accuracy were found to be less than 11.7 and 8.8%, respectively.

HPLC-UV Method for Human Plasma[25]

A simple HPLC method with UV detection for the quantification of lacosamide in human plasma. The method involves protein precipitation with methanol followed by chromatographic separation using an ACE® C-18-AR column (2.1 mm × 150 mm, 3.0 µm) and mobile phases consisting of mixtures of ammonium formate buffer at pH 9 and acetonitrile. Briefly, 25 µl of internal standard and 300 µl of methanol are added to 100 µl of plasma. After vortexing and centrifugation, 70 µl of supernatant is transferred to an autosampler vial and 5.0 µl is injected. Calibration curves are linear in the range of 0.5 to 12.5 µg/ml. A validation was performed that consisted of the evaluation of accuracy and precision, specificity, limit of detection and carryover. Moreover, the possibility of using single-point calibration was evaluated and a cross validation between this method and an established LC-MS/MS method using pooled clinical study samples was performed. The method's sensitivity, simplicity and reliance on simpler HPLC equipment should allow for straightforward application in drug monitoring.

HPTLC Method[29]

`A new, economic, precise and rapid high-performance thin-layer chromatographic (HPTLC) method was developed and validated for quantitative determination of Lacosamide. The HPTLC separation was achieved on an aluminium-backed layer of silica gel 60F254 using toluene: methanol (7.5ml : 2.5ml, v/v) as mobile phase. Quantitation was achieved by densitometric analysis at 258 nm over the concentration range of 2000-12000 ng/spot. The method was found to give compact spot for the drug (Rf 0.55). The linear regression analysis data for the calibration plots showed good linear relationship with r2 = 0.9972. The minimum detectable amount was found to be 364.88 ng/spot, whereas the limit of quantitation was found to be 1105.72 ng/spot.

CONCLUSION

Lacosamide is a new antiepileptic drug with two novel mechanisms of action that may be suitable for use with partial-onset epilepsy. Its pharmacokinetic profile is favourable, and the drug does not appear to have potentially severe adverse effects. The potential for drug interactions with other antiepileptic drugs and currently prescribed drugs are very low. This makes lacosamide a promising new drug for adjunctive treatment for partial-onset seizures. Lacosamide is being investigated as a treatment option for diabetic neuropathic pain, fibromyalgia, and migraine prophylaxis. With its novel mechanism of action and favorable pharmacokinetic and safety profile, there is no doubt that we will be seeing more of this drug in the future.

Various analytical methods for determining lacosamide has been developed to monitor its action in human as well as animal models. Analytical methods for quality control of lacosamide in its different pharmaceutical formulations also been reported. New analytical techniques are under development for determination of this new antiepileptic drug.

REFERENCES

1. www.epilepsy.com › ... › 2008 › November 2008 Newsletter
2. http://www.epilepsyindia.org/home.asp
3. Halford et al. Clinical Perspectives on Lacosamide. Epilepsy Currents. 2009; 9(1): 19.
4. en.wikipedia.org/wiki/Lacosamide
5. www.nlm.nih.gov/medlineplus/druginfo/meds/a609028.html
6. Vimpat® Approved in Europe. Available at http://wwwucbcom/news/3606asp. UCB, Inc. Press Release September 3, 2008.
7. Vimpat [package insert]. Smyrna, GA: UCB, Inc; 2011.
8. Kelemen and Halasz. Lacosamide for the Prevention of Partial Onset Seizures in Epileptic Adults. Neuropsychiatric Disease and Treatment. 2010; 6: 465 - 471.
9. Beyreuther BK, Freitag J, Heers C, Krebsfanger N, Scharfenecker U, Stöhr T. Lacosamide: A review of preclinical properties. CNS Drug Rev. 2007;13:21- 42. [PubMed]

10. Doty P, Rudd GD, Stoehr T, Thomas D. Lacosamide. Neurotherapeutics. 2007;4:45-148. [PubMed]
11. Andurkar SV. The anticonvulsant activities of N-benzyl 3-methoxypropionamides. Bioorg Med Chem. 1999;7:2381–2389. [PubMed]
12. Errington AC, Coyne L, Stöhr T, Selve N, Lees G. Seeking a mechanism of action for the novel anticonvulsant lacosamide. Neuropharmacology. 2006;50:1016 -1029. [PubMed]
13. Heers C, Lees G, Errington A, Stoehr T. Lacosamide selectively enhances sodium channel slow inactivation. Epilepsia. 2007;48:320.
14. Errington A, Stöhr T, Heers C, Lees G. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. Mol Pharmacol. 2008;73:157 - 169. [PubMed]
15. Freitag JM, Beyreuther B, Heers C, Stoehr T. Lacosamide modulates collapsin response mediator protein 2 (CRMP-2) Epilepsia. 2007;48:320.
16. Stöhr T, Kupferberg HJ, Stablesa JP, Choid D, Harris RH, Kohnf H, Waltong N, White HS. Lacosamide, a novel anti-convulsant drug, shows efficacy with a wide safety margin in rodent models for epilepsy. Epilepsy Res. 2007;74:147 -154. [PubMed]
17. Stöhr T, Baldwin R, Walton N, Wasterlain CG. Lacosamide is anticonvulsive and neuroprotective in rat models for self-sustaining status epilepticus. American Epilepsy Society Meeting; New Orleans, LA. 2004.
18. Sai Sumanth K, Jose Gnana Babu C, Ulaganathan, Muneer S, Balaji M. Validated spectrophotometric estimation of lacosamide in bulk and its tablet dosage form. International Journal of Pharmaceutical Research & Analysis. 2012; Vol 3(11): 78-82.
19. Ganji Ramanaiah D, Ramachandran, Srinivas G, Srilakshmi, Purnachanda Rao. Development and validation of UV spectroscopy method for estimation of lacosamide in bulk and formulations. Int J Pharm Biomed Sci. 2012; 3(1): 10 -12.
20. Vudagandla Sreenivasulu, Dokku Raghava Rao, Uma Maheswari BN , Samar K Das, Abburi Krishnaiah. Development and validation of a stability-indicating RP - HPLC method for determination of lacosamide Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2011; 2 (4): 1-11.
21. Sai Sumanth K, Jose Gnana Babu1 C, VenkataMahesh K, Muneer S, Balaji M. Development and validation of RP-HPLC method for estimation of lacosamide in bulk and its pharmaceutical dosage form International Journal of Pharmaceutical Research & Analysis. 2011; 2(1): 1-5.
22. Usmangani K. Chhalotiya Kashyap, K. Bhatt Dimal, A. Shah, Sunil L. Baldania, Jigar R. Patel. Stability-indicating liquid chromatographic method for quantification of new anti-epileptic drug lacosamide in bulk and pharmaceutical formulation. Chemical Industry & Chemical Engineering Quarterly. 2012;18 (1): 35- 42.
23. Ramanaiah Ganji, Ramachandran D , Srinivas G, Srilakshmi V, Purnachanda Rao. Development and Validation of Stability Indicating RP-LC Method for Estimation of Lacosamide in Bulk and Its Pharmaceutical Formulations. Am. J. PharmTech Res. 2012; 2(2).
24. Soo-Jin Kim, Tae-Sung Koo, Dong-Jin Ha, Myoungki Baek, Sang-Kil Lee, Dong-Soo Shin, Hongsik Moon. Liquid chromatography–tandem mass spectrometry for quantification of lacosamide, an antiepileptic drug,

in rat plasma and its application to pharmacokinetic study. Biomed Chromatogr. 2012 Mar ;26 (3):371-6.
25. Kestelyn C, Lastelle M, Higuet N, Dell'Aiera S, Staelens L, Boulanger P, Boekens H, Smith S. A simple HPLC-UV method for the determination of lacosamide in human plasma. Bioanalysis. 2011 Nov;3 (22):2515 - 22.
26. JoEtta M. Juenke , Paul I. Brown, Ronald L Thomas , and Kamisha L. Johnson -Davis. Application of ultra high-performance liquid chromatography tandem mass spectrometry for the analysis of lacosamide and metabolite des-lacosamide, rufinamide, and felbamate in serum and plasma. ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT.USA, Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT USA.
27. Kalyan ChakravarthyV and Gowri Shankar D. HPLC method for determination of lacosamide s(-)enantiomer in bulk and pharmaceutical formulation Rasayan Journal of chemistry. 2011; 4(3) :744 - 752.
28. Kalyan Chakravarthy V and Gowri Sankar D. Development and Validation of RP-HPLC method for estimation of lacosamide in bulk and its pharmaceutical formulation Rasayan Journal of Chemistry. 2011; 4(3): 666 - 672.
29. Kamdar S A, Vaghela V M, Desai P A. Development and Validation of HPTLC Method for Estimation of Lacosamide in Bulk Drug and in Tablet Dosage Form PMID:20736895 [PubMed - indexed for MEDLINE].
30. Sethi P D, HPLC-Quantitative Analysis of Pharmaceutical Formulations, First Edition, CBS Publishers and Distributors;12 - 119.
31. Hobart.H.Willard, Lynne.L.Merritt, John.A.Dean, Frank.A.Settle, Instrumental Methods of Analysis ,Seventh Edition, CBS Publishers and Distributors; 118 - 608.
32. Kenneth.A.Connors, A Textbook of Pharmaceutical Analysis, Third Edition,John Wiley & Sons; 418 - 421.
33. Satinder Ahuja & Stephen Soypinski, Handbook of Modern Pharmaceutical Analysis, Academic Press; Vol 3,349 – 366.
34. Chung. New Treatment Option for Partial-Onset Seizures: Efficacy and Safety of Lacosamide. Ther Adv Neurol Disord. 2010: 3(2): 77 - 83.
35. Kellinghaus. Lacosamide as Treatment for Partial Epilepsy: Mechanisms of Action, Pharmacology, Effects and Safety. Therapeutics and Clinical Risk Management. 2009; 5:757 - 766.
36. Abou-Kalil. Lacosamide: What can be expeted from the next new antiepileptic drug? Epilepsy Currents. 2009; 9(5): 133 - 134.
37. http://www.wmshp.net/viewnews.php?article=108
38. Heers C, Lees G, Errington A, Stoehr T. Lacosamide selectively enhances sodium channel slow inactivation. Epilepsi.a 2007; 48:320.
39. Lees G, Stohr T, Errington AC. Stereoselective effects of the novel anticonvulsant lacosamide against 4-AP induced epileptiform activity in rat visual cortex in vitro.Neuropharmacology. 2006;50:98 - 110.
40. Thomas D, Doty P, Scharfenecker U, Horstmann R, Nickel B, Yates S. Lacosamide has low potential for drug-drug interaction. American Epilepsy Society Meeting. Philadelphia, PA, 2007.