Case Report
Journal of Epilepsy Research
pISSN 2233-6249 / eISSN 2233-6257

The Use of Perampanel in the Treatment of Lance-Adams Syndrome

Vishal Pandya, MD[1], Khalil S. Husari, MD[2]

[1]*Department of Neurology, Comprehensive Epilepsy Center, Medical College of Wisconsin, Milwaukee, WI, USA;*
[2]*Department of Neurology, Comprehensive Epilepsy Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Received March 27, 2024
Revised July 14, 2024
Accepted August 6, 2024

Corresponding author:
Vishal Pandya, MD
Department of Neurology, Comprehensive Epilepsy Center, Medical College of Wisconsin, Milwaukee, WI 53226, USA
Tel. +1-414-805-8710
Fax. +1-414-805-1101
E-mail; vpandya@mcw.edu

Lance Adams syndrome (LAS) is characterized by chronic action or intention myoclonus resulting from cerebral hypoxia. Perampanel, a non-competitive antagonist of aamino-3-hydroxy-5methyl-4 isooxazoleproprionic acid glutamate receptor, has demonstrated some efficacy in myoclonic epilepsy and other types of myoclonus. We report significant benefit in a patient with LAS treated with add on perampanel and provide a review of the relevant literature. In our case, a male patient in his 30s was found pulseless with unknown down time. The patient developed post anoxic myoclonus within 1 week from cardiac arrest. Patient continued to suffer from intractable myoclonus despite being treated with brivaracetam, valproic acid, and clonazepam. Perampanel was added to his medication regimen and up-titrated to 12 mg daily over 1-2 weeks. This resulted in significant improvement in frequency and severity of myoclonus for about 6 months. Growing evidence exists for perampanel as an adjunctive treatment in patients with post hypoxic myoclonus or LAS. A review of the available literature, comprised of case reports and case series, and suggests a potential role for perampanel in patients with LAS. Further study is warranted including controlled trials of perampanel use in post hypoxic myoclonus. **(2024;14:97-101)**

Key words: Perampanel, Lance- Adams syndrome, Anti seizure medication, Epilepsy, Seizure, Myoclonus

Introduction

Lance Adams syndrome (LAS) is characterized by chronic action or intention myoclonus resulting from cerebral hypoxia occurring in about 0.5% of patients.[1] Clinical presentation is usually 48 hours to several weeks after the anoxic injury.[2] The myoclonus is activated by movement and tactile stimulation and abates with rest. There are no controlled studies assessing treatment of LAS.[2] Treatment response has been reported with several antiseizure medications including valproic acid, levetiracetam, lacosamide, and clonazepam.[3-5] However, the myoclonus in LAS can be quiet disabling and refractory to several medications, with frequently partial response.[2]

Perampanel, a non-competitive antagonist of amino-3-hydroxy-5methyl-4 isooxazoleproprionic acid (AMPA) glutamate receptor,[6] has demonstrated some efficacy in myoclonic epilepsy[7,8] and other types of myoclonus. Here, we report significant benefit in a patient with LAS treated with add on perampanel and provide a brief review the relevant literature regarding the use of perampanel in Lance-Adams syndrome.

Case Report

A male patient in his 30s was found pulseless with unknown down time. Initially, he was in ventricular fibrillation which progressed to asystole, then pulseless electrical activity. Return of spontaneous circulation was achieved after about 20 minutes from initial resuscitation. Initial electoencephalography (EEG) revealed near continuous generalized periodic discharges with spike-wave morphology at about 2-2.5 Hz with frequent evolution into electroclinical seizures, consistent with post anoxic status epilepticus. The patient was treated with intravenous anesthetics, levetiracetam, lacosamide, and valproic acid. The patient developed post anoxic myoclonus within 1 week from cardiac arrest. Anti-seizure medication doses were adjusted with marginal improvement. After prolonged hospitalization, the patient was discharged to a rehabilitation facility with a cerebral performance category scale of 3 and a Glasgow outcome scale of 3.

The patient continues to suffer from intractable myoclonus despite being treated with multiple anti-seizure medications including brivaracetam, valproic acid, and clonazepam. Nine months following initial

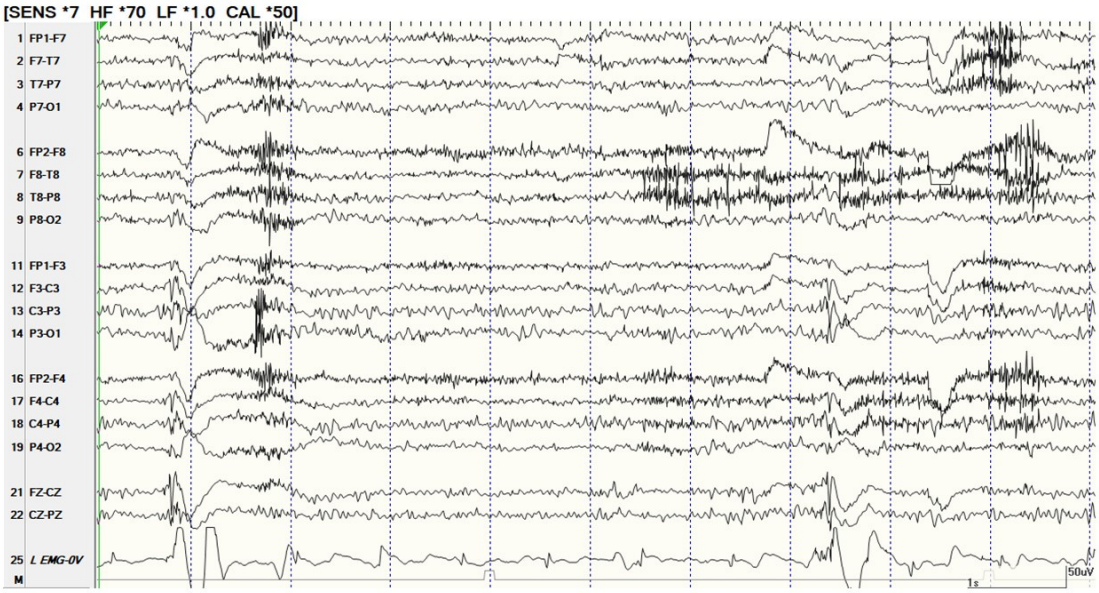

Figure 1. A bipolar montage EEG with an additional EMG chain placed on the patient's left arm, showing two bilateral central maximum spike waves with time-locked myoclonus (artifact in the EMG chain). Please note that the EMG chain is contaminated with EKG artifact. HF, high frequency; LF, low frequency; CAL, calibration; FP, frontopolar; F, mid frontal; T, mid temporal; P, parietal; O, occiptal; C, central; FZ, midline frontal; CZ, midline central; PZ, midline parietal; LEMG, left electromyogram electrode; EEG, electoencephalography; EMG, electromyography; EKG, electrocardiogram.

anoxic insult, the patient was admitted for anti-seizure medication management. Continuous video EEG revealed bilateral central maximum spike and polyspike and slow wave complexes in waking and sleep and innumerable epileptic myoclonic jerks. Electrographically, the myoclonic jerks were preceded by bilateral synchronous spike and polyspike and wave complexes (Fig. 1). Perampanel was gradually added to his medication regimen. Perampanel was up-titrated to 12 mg daily over 1-2 weeks. This has resulted in significant improvement in frequency and severity of myoclonus for about 6 months. The patient tolerated perampanel without major adverse effects.

Discussion

Perampanel is currently indicated as adjunctive therapy and monotherapy for focal seizures, as well as adjunctive treatment for primary generalized tonic-clonic seizures.[6] In this case report, we add to the body of literature supporting the use of perampanel in treating refractory Lance-Adams syndrome.

Perampanel is the first selective noncompetitive AMPA receptor antagonist to be successfully developed to treat epilepsy.[6] The efficacy and safety of perampanel was demonstrated in three large randomized control trials and extension studies.[9-13] A dose of 4 mg/day was found to be the lowest effective dosage and doses of 8 mg/day and 12 mg/day were effective against placebo with only moderate increase in efficacy at 12 mg/day when compared to 8 mg/day. Utilizing pooled data, the reduction in mean seizure frequency were 23.3% at 4 mg/day, 28.8% at 8 mg/day, and 27.2% for 12 mg/day dose groups. Responder rates were 28.5% for 4 mg/day, 35.3% for 8 mg/day, and 35% for 12 mg/day.[6]

In general, myoclonus can be classified by its pathophysiologic etiology and by its clinical presentation. In the former case, this classification includes cortical myoclonus, cortical- subcortical myoclonus, subcortical/nonsegmental myoclonus, segmental myoclonus, and peripheral myoclonus.[14] Classification by clinical presentation includes physiologic myoclonus, essential myoclonus, epileptic myoclonus, and symptomatic myoclonus (progressive myoclonic epilepsy syndromes, neurodegeneration, inflammation, metabolic conditions, drug induced, and post hypoxia).[14]

There have been several case reports and case series that have demonstrated the efficacy of perampanel in progressive myoclonic epilepsies,[7,8] non-epileptic myoclonus, in refractory status epilepticus,[15] including post-anoxic myoclonic status epilepticus,[16,17] and in Lance-Adams syndrome.[18-27]

The pathophysiological mechanism of LAS is unclear but has been

Table 1. Reported cases of using perampanel in Lance Adams syndrome

Stady	N	Demographics	Clinical features	Dose of PRM	ASMs used concurrently with PRM	Effect on myoclonus	Adverse effects
Steinhoff et al. (2016)[19]	1	36 male	Post-hypoxic myoclonus for 1 year, Brugada syndrome	2 mg daily increased to 4 mg daily	None	Suppression of myoclonic jerks on 4 weeks follow up	Somnolence
López et al. (2017)[10]	1	35 male	Three consecutive cardiac arrests	24 mg daily	-Levetiracetam, valproate, propofol, sodium thiopental, zonisamide, 5HT, piracetam, clonidine, and sodium oxybate -Discharged on levetiracetam, gabapentin, and perampanel	Myoclonus improved	Behavioral disorders (added risperidone)
Yelden et al. (2019)[22]	2	69 male	Anoxic injury following severe pneumonia	Not provided	Lev, valproate, and clonazepam (reduced dose)	Improvement in myoclonic jerks and functional abilities	N/A
		37 female	Anoxic injury following accidental decannulation of tracheostomy tube	N/A	Levetiracetam	Improvement in myoclonic jerks and functional abilities	N/A
Lim et al. (2020)[21]	1	63 male	Cardiac bypass surgery complicated postoperatively by cardiac arrest	2 mg daily for 1 week, then 4 mg daily	Levetiracetam, clonazepam, valproate, and acetazolamide	Resolution in myoclonus and gait improvement	N/A
Stubblefield et al. (2021)[23]	4	28 female	Septic shock and asystolic arrest with hypoxic injury	4 mg three times daily	Clobazam, valproate, and phenytoin	Near cessation of myoclonus	None
		75 male	Mucous plug and hypoxic injury due to PEA	4 mg nightly	Valproate (levetiracetam and clonazepam stopped after response to perampanel)	Near-full abatement of myoclonic jerks	None
		29 male	MVA, blood loss, and cardiac arrest	4 mg nightly	Clobazam	Complete resolution of myoclonus	Cognitively impaired unable to report SEs
		36 male	History of hypoxic events developed non-epileptic myoclonus involving the trunk, extremities, head, neck, and consistent with LAS	4 mg twice daily increased to three times daily	Levetiracetam (lamotrigine and carbamazepine stopped after response to perampanel)	Significant improvement in myoclonus	None
Katsuki et al. (2021)[24]	1	65 male	Sudden cardiac arrest	2 mg daily increased to 4 mg daily and 10 mg to 8 mg daily	Levetiracetam and lacosamide	Resolution of myoclonus	N/A
Saita et al. (2022)[26]	1	22 female	Attempted suicide by hanging resuscitated from cardiopulmonary arrest	2 mg daily increased to 4 mg daily	Levetiracetam and valproate	Resolution of difficulty walking due to myoclonus	N/A
Current case report	1	30 male	V Fib cardiac arrest	12 mg daily	Brivaracetam, valproic acid, and clonazepam	Significant improvement in myoclonus for 6 months	None

PRM, perampanel; ASMs, anti seizure medications; 5HT, 5-hydroxytryptamine; N/A, non applicable; PEA, pulseless electrical activity; MVA, motor vehicle accident; SEs, side effects; LAS, Lance Adams syndrome; V Fib, ventricular fibrillation.

hypothesized to originate in the cortex/subcortex. The generation of myoclonus is thought to be due to abnormal levels of neurotransmitters, abnormal low levels of serotonin and gamma-amino butyric acid (GABA).[28,29] Treatment with L-5-hydroxytryptophan (a serotonin precursor) demonstrated some success in controlling myoclonus and is thought to do so by increasing the low levels of serotonin. Anti-seizure medications such as benzodiazepines and valproate have been efficacious in cases of LAS due to their increasing levels of GABA in the synapse.[30]

The mechanism by which perampanel appears to be an effective adjunctive treatment in LAS is unclear. Perampanel works on excitatory glutamatergic neurons. Perampanel works to modify the synaptic transmission at the cortical-subcortical level and may decrease excitation at the synaptic level.[31] A subset of patients with cortical myoclonus demonstrated giant somatosensory evoked potential (SEP) reflecting cortical hyperexcitability.[32] One study showed that patients who responded to low dose perampanel had a decrease in the amplitude and increase in the latency of giant SEP (temporal dispersion). The authors hypothesized based on the SEP findings that perampanel inhibited and dispersed epileptic cortical hyperexcitability with hyper-synchronization in the primary motor cortex.[33]

While there have not been any controlled studies assessing the efficacy of perampanel in LAS, multiple case reports and case series supporting its efficacy do exist.[5-14] In Table 1 below we have summarized the results of these studies.

Growing evidence exists for perampanel as an adjunctive treatment in patients with post hypoxic myoclonus or LAS. Perampanel has been used effectively to treat other forms of myoclonus including those in progressive myoclonic epilepsies, non-epileptic myoclonus, and in refractory status epilepticus including post-anoxic myoclonic status epilepticus. This brief review of the available literature, though limited to case reports and case series, suggests a potential role for perampanel in patients with LAS. Further study is certainly warranted including controlled trials of perampanel use in post hypoxic myoclonus.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

References

1. Lance JW, Adams RD. The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain* 1963;86:111-36.
2. Gupta HV, Caviness JN. Post-hypoxic myoclonus: current concepts, neurophysiology, and treatment. *Tremor Other Hyperkinet Mov (N Y)* 2016;6:409.
3. Wicklein EM, Schwendemann G. Use of clonazepam and valproate in patients with Lance Adams syndrome. *J R Soc Med* 1993;86:618.
4. Ilik F, Kemal Ilik M, Cöven I. Levatiracetam for the management of Lance-Adams syndrome. *Iran J Child Neurol* 2014;8:57-9.
5. Galldiks N, Timmermann L, Fink GR, Burghaus L. Posthypoxic myoclonus (Lance-Adams syndrome) treated with lacosamide. *Clin Neuropharmacol* 2010;33:216-7.
6. Krauss GL. Perampanel: a selective AMPA antagonist for treating seizures. *Epilepsy Curr* 2013;13:269-72.
7. Dirani M, Nasreddine W, Abdulla F, Beydoun A. Seizure control and improvement of neurological dysfunction in Lafora disease with perampanel. *Epilepsy Behav Case Rep* 2014;2:164-6.
8. Schorlemmer K, Bauer S, Belke M, et al. Sustained seizure remission on perampanel in progressive myoclonic epilepsy (Lafora disease). *Epilepsy Behav Case Rep* 2013;1:118-21.
9. Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. *Neurology* 2012;78:1408-15.
10. López EL, Urbina MJ, Sónchez AP, et al. DI-096 refractory lance-adams syndrome: pharmacotherapy management and iatrogenic complications. *BMJ* 2017;24:A156.
11. French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. *Epilepsia* 2013;54:117-25.
12. Krauss GL, Perucca E, Ben-Menachem E, et al. Perampanel, a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. *Epilepsia* 2013;54:126-34.
13. Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. *Epilepsia* 2013;54:1481-9.
14. Caviness JN. Myoclonus. *Continuum (Minneap Minn)* 2019;25:1055-80.
15. Newey CR, Mullaguri N, Hantus S, Punia V, George P. Super-refractory status epilepticus treated with high dose perampanel: case series and review of the literature. *Case Rep Crit Care* 2019;2019:3218231.
16. Santamarina E, Sueiras M, Lidón RM, et al. Use of perampanel in one case of super-refractory hypoxic myoclonic status: case report. *Epilepsy Behav Case Rep* 2015;4:56-9.
17. Beretta S, Padovano G, Stabile A, et al. Efficacy and safety of perampanel oral loading in postanoxic super-refractory status epilepticus: a pilot study. *Epilepsia* 2018;59 Suppl 2:243-8.
18. Guo Y, Xiao Y, Chen LF, Yin DH, Wang RD. Lance Adams syndrome: two cases report and literature review. *J Int Med Res* 2022;50:300060 5211059933.
19. Steinhoff BJ, Bacher M, Kurth C, Staack AM, Kornmeier R. Add-on perampanel in Lance-Adams syndrome. *Epilepsy Behav Case Rep* 2016;6:28-9.

20. Lim ML, Lim RRZ, Tien JC, Lim SZZ, Lee YL. Lance Adams syndrome after hypoxic cardiac arrest: a case report. *A A Pract* 2022;16:e01605.
21. Lim SY, Jasti DB, Tan AH. Improvement of "bouncy gait" in Lance-Adams syndrome with perampanel. *Cureus* 2020;12:e6773.
22. Yelden K, Rendell L, Vardy L, Rose A, Crilly S, Merrison K. Treatment of refractory myoclonus with perampanel in Lance Adams syndrome: a report of two cases. *Brain Inj* 2019;33:1-337.
23. Stubblefield K, Zahoor S, Sonmezturk H, Haas K, Mattingly D, Abou-Khalil B. Perampanel is effective against Lance-Adams syndrome. *Epileptic Disord* 2021;23:769-71.
24. Katsuki M, Narita N, Yasuda I, Tominaga T. Lance-Adams syndrome treated by perampanel in the acute term. *Cureus* 2021;13:e13761.
25. Kamel WA, Al-Hashel JY, Abdulsalam AJ, Arabi M. Perampanel in refractory post-hypoxic myoclonus: see the difference! *Acta Neurol Belg* 2020;120:741-2.
26. Saita D, Oishi S, Saito M. Administration of a small dose of perampanel improves walking ability in a case of Lance-Adams syndrome. *Psychiatry Clin Neurosci* 2022;76:89.
27. Muro-García I, Vieira A, Vega L, Pastor J, de Toledo M. Response to perampanel in a patient with chronic post-hypoxic myoclonus. *Rev Neurol* 2021;73:111-3.
28. Werhahn KJ, Brown P, Thompson PD, Marsden CD. The clinical features and prognosis of chronic posthypoxic myoclonus. *Mov Disord* 1997;12:216-20.
29. Matsumoto RR, Truong DD, Nguyen KD, et al. Involvement of GABA(A) receptors in myoclonus. *Mov Disord* 2000;15 Suppl 1:47-52.
30. Frucht SJ, Trost M, Ma Y, Eidelberg D. The metabolic topography of posthypoxic myoclonus. *Neurology* 2004;62:1879-81.
31. Yang YC, Wang GH, Chuang AY, Hsueh SW. Perampanel reduces paroxysmal depolarizing shift and inhibitory synaptic input in excitatory neurons to inhibit epileptic network oscillations. *Br J Pharmacol* 2020;177;5177-94.
32. Anzellotti F, Onofrj M, Bonanni L, Saracino A, Franciotti R. Giant early components of somatosensory evoked potentials to tibial nerve stimulation in cortical myoclonus. *Neuroimage Clin* 2016;12:212-8.
33. Oi K, Neshige S, Hitomi T, et al. Low-dose perampanel improves refractory cortical myoclonus by the dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex. *Clin Neurophysiol* 2019;130:1804-12.