



Published in final edited form as:

Epilepsy Behav. 2016 September ; 62: 132–135. doi:10.1016/j.yebeh.2016.06.041.

Efficacy and Tolerability of Perampanel in Ten Patients with Lafora Disease

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Summary

Lafora disease (LD) is a fatal intractable adolescence-onset progressive myoclonus epilepsy. Recently, two single-case studies reported drastic reductions in seizures and myoclonus with the AMPA antagonist perampanel, and improved activities of daily living. We proceeded to study the effect of perampanel on 10 genetically confirmed LD patients with disease duration ranging from 2 to 27 years. Open-labeled perampanel was added to ongoing medications to a mean dose of 6.7 mg/day. Seizures, myoclonus, functional disability and cognition scores were measured for the third and ninth month following initiation and compared to the month prior to start of therapy. Three patients withdrew due to inefficacy or side-effects. Four had significant reduction in seizures of greater than 74% from baseline. Seven had major improvement in myoclonus with group-adjusted sum score of myoclonus intensity reduced from 7.01 at baseline to 5.67 and 5.18 at 3 and 9 months respectively. There was no significant improvement in disability and cognition. While not universal, perampanel adjunctive therapy appears to confer particular benefit not commonly seen with other anti-epileptic drugs on seizures and myoclonus in LD. Improvement in the extremely disabling myoclonus of LD is a major benefit in this devastating disease.

Keywords

Lafora disease; progressive myoclonus epilepsy; perampanel; antiepileptic

Introduction

Lafora disease (LD) is a fatal progressive myoclonus epilepsy (PME) that strikes previously healthy adolescents. Seizures and myoclonus increasingly worsen and become intractable, while the patient's physical and mental functions gradually fail. Death occurs usually within a decade from symptom onset, commonly in status epilepticus¹. LD is an autosomal recessive disease caused by mutations in either the *EPM2A* or *EPM2B* gene, which encode

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Disclosure of Conflicts of Interest: None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

the laforin glycogen phosphatase and the malin ubiquitin E3 ligase, respectively²⁻³. These enzymes play essential roles in glycogen metabolism, specifically in ensuring glycogen's spherical architecture. With loss of function of either, glycogen becomes malformed (starch-like, with reduced branching and excessively long chains) and insoluble. It gradually precipitates, aggregates, and accumulates to form Lafora Bodies (LB) in many cell types, including in the cell bodies and dendritic spaces of neurons, the latter likely underlying the inexorable progression of the epilepsy⁴.

By the fifth year following first symptoms, most LD patients are on multiple anti-epileptic drugs (AEDs), almost invariably including valproic acid, but they continue to experience disabling seizures and myoclonus. Two recent single case studies reported the effects of the relatively new AED and selective AMPA receptor antagonist perampanel in LD. The drug appeared to lead to sustained remission in myoclonus and generalized tonic-clonic seizures⁵⁻⁶. In the first case, a 21 year-old Turkish girl with an *EPM2A* mutation, adjunctive therapy with 8 mg/day of perampanel led to dramatic reduction in seizure and myoclonus frequency over three months. When the dose was reduced seizures recurred, only to re-disappear for three months of follow-up when the dose was again increased. The patient's walking ability also improved⁵. In the second case, an 18 year-old Bahraini girl with an *EPM2B* mutation, perampanel monotherapy was titrated to 10 mg/day. The patient experienced drastic improvement in frequency of myoclonus and generalized seizures. Further, she was able to walk again and perform daily tasks. These improvements were sustained over an observation period of seven months.⁶ The aim of our study was to determine the therapeutic effects of perampanel in a group of ten patients using uniform outcome measures. Specifically, we assessed the frequencies and severities of seizures and myoclonus and activities of daily living over a period of ten months, compared to a pre-treatment baseline period.

Methods

Patients with genetically confirmed LD were enrolled in our open-label, multi-center study after informed consent was obtained. Study participants were found through Chelsea's Hope Lafora Children Research Fund, one of the largest networks for families affected by LD worldwide. Because of the rarity of LD, we accepted patients from multiple countries, and because of the difficulty of transporting patients with LD, they were treated and assessed locally by their caretakers, family members and personal clinicians. The first patient was entered into the study in January 2015. Patients were assessed by their caregivers prior to initiation of perampanel in order to obtain a comparative baseline. Treatment initiation with perampanel began at a dose of 2mg/day and was increased at a rate of 2mg/day every 1-2 weeks. Perampanel was titrated to an individual therapeutic dose depending on tolerability and clinical response, up to 12 mg/day. Patients remained on the same concomitant AED regimen as they had previously received; some dose adjustments were made by the patient's treating physician when clinically indicated. After starting treatment with perampanel, patients were followed for up to ten months. Caretakers were asked to keep track of the number of generalized tonic-clonic seizures (GTCS), defined as large convulsions involving most or all of the body, experienced by the patients during the previous 28-day period prior

to evaluation time points. The averages and percent change in GTCS frequency from the baseline period was calculated.

Apart from recording the frequency of GTCS, caregivers were asked to complete surveys at baseline, 2-3 and 9-10 months in which they reported: (1) myoclonus frequency, severity, amplitude and intensity, and (2) level of functional disability and cognitive performance. We wrote the survey with help from caregivers in order to determine the best possible measurement outcomes. We distinguished myoclonus from generalized tonic-clonic seizures because they are both present to varying degrees in LD. We defined myoclonus as sudden jerks or twitches that occur in groups of muscles, whereas GCTS are larger, more convulsive-like seizures. Myoclonus was assessed using numerical scales based on a modified version of the Unified Myoclonus Rating Scale (UMRS).⁷ Levels of ability across functional domains were assessed separately of myoclonus to determine the effects of perampanel on daily living tasks and to paint a more accurate picture of the stage of disease of each patient. Myoclonus factors and functional domains are indicated in Table 1. A quantitative adjusted sum score was calculated based on the results of the survey. Adverse Events (AEs) were reported throughout the study. Due to withdrawals during the study, an Intention-to-Treat analysis was used to compare baseline and treatment measurements.

Results

Ten patients were enrolled with a mean age of 22.5 years. The mean number of years since appearance of first symptoms was 8.3. Eight of the patients were female and two were male. The mean dose maintained by patients at final evaluation was 6.7 mg/day. Two patients reduced their daily dose by 2 mg after reaching their maximum titrated dose due to negative side effects (mood changes, agitation, increased hallucinations). The reduction in dose ameliorated mood swings in one of the patients, but did not decrease hallucinations in the other. By the end of the study, seven patients had >9 months exposure to perampanel treatment. Three patients discontinued treatment at 2-6 months of treatment due to undesired effects or lack of efficacy. Patients 5, 8 and 10 from Table 2 were taken off treatment at dosages of 4 mg, 8 mg and 4 mg, respectively. Adverse effects were reported in eight patients. AEs included: trouble sleeping, irritability, aggression, somnolence, vision impairments, increased hallucinations, headaches, nervousness, depressed mood, loss of mobility and loss of coordination. No serious AEs were reported as being associated with perampanel treatment.

Four patients had a reduction in GTCS frequency, with mean percentage drop per 28 days at 2-3 and 9-10 months after exposure to perampanel of 74% compared to baseline. The frequency of GTCS worsened in two patients by an average increase of 95% relative to baseline. One of the patients did not suffer from GTCS at all, and thus did not have an increase or decrease in GTCS frequency (Table 3). In the overall group, average number of GTCS per 28 days reported at baseline was 6.14 (range 0-25). At the evaluation times of 2-3 and 9-10 months, the average number of GTCS was reduced to 2.29 (range 0-6) and 2.86 (range 0-10), respectively. Seven patients had improvement in myoclonus. The group mean adjusted sum score of myoclonus intensity at baseline was 7.01 compared to 5.67 and 5.18 at 2-3 months and 9-10 months, respectively. There was no significant change in functional

or cognitive measures. The mean adjusted sum score of functional disability at baseline was 8.3 compared to 7.8 and 7.7 at 2-3 months and 9-10 months, respectively (Table 3).

Discussion

LD is an invariably fatal teenage-onset PME characterized by relentless ever-worsening myoclonus, seizures, and dementia. The lack of a therapy against the disease itself and the inexorable progression and protracted suffering are agonizing to both patients and families (including at-risk younger siblings). Any extent of symptom relief is therefore highly desirable. Our study aimed at testing the benefits reported in two separate single case studies in a larger cohort. We recruited the patients without consideration of which LD gene was affected, and find that all but one have *EPM2A* mutations. In the general population, LD patients are equally divided between those with *EPM2A* and *EPM2B* mutations.⁸ The skewing towards *EPM2A* in our study is likely simply a chance event. It cannot be explained by greater severity or earlier fatality of the *EPM2B* genotype, because, if anything, *EPM2B* patients have a slightly slower disease course.⁹ LD is a rare disease with an incidence estimated between 1/200,000 and 1/1,000,000.¹⁰ However, the connectivity of the modern world and extreme severity of the disease have led many families to be close. Publication of the two case studies showing efficacy for perampanel⁵⁻⁶ drove the community to request the medication for their children from their neurologists. We decided to take advantage of this and organize the present study. Our results are in general accord with the two case reports. In our overall group of patients both seizures and myoclonus improved, the latter more than the former. Seizure frequency did not diminish in all patients, and in fact worsened in two. This worsening, however, is difficult to separate from the progressive nature of the disease. In the patients who did respond, the response was impressive with up to 95% seizure reduction in two patients.

The constant positive and negative myoclonus, accompanied by thought interruption (myoclonic absence), occurring continuously through wakefulness, is the most disabling symptom in LD. It remains difficult to accurately quantify myoclonus on a clinical basis without the use of simultaneous VEEG, so it must be acknowledged that there are limitations to our myoclonus scale. That being said, according to evaluations and caregiver interviews, it appears myoclonus did improve substantially in the majority of the patients.

Of course our study was open-label and not placebo-controlled and thus susceptible to biases. These, however, are unlikely to arise from the side of the patient in this epilepsy, because most of these patients are on multiple drugs as it is and cognitively impaired. As for the families, while they are driven with hope, they generally also have both high realism about the nature of the disease and resistance to staying on yet more medications if these do not show real benefit. A second limitation of our study is that the data was not collected by neurologists or related professionals, but by immediate caregivers. However, it must be said that these caregivers have the most intimate and continuous knowledge of each individual patient, and may well be able to see subtle day-to-day changes that a physician cannot.

To our knowledge there has never been a trial of any AED in any group of LD patients. Experience and general principles have led clinicians to preferentially use medications with

efficacy in generalized epilepsy, such as valproic acid and levetiracetam, and most clinicians refrain from using medications with activity restricted to focal-onset epilepsies. Perampanel was originally developed for focal-onset epilepsy, but recent studies have shown its spectrum to strongly extend to generalized epilepsy¹¹, and our study appears to support this extension to PME, at least to LD.

Although the previous case studies reported improvements in functional abilities, in our study the adjusted sum score for functional and cognitive impairment did not provide any evidence of this. Observed adverse effects by caregivers were relatively mild and tolerable. No serious adverse effects were reported. However, side effects were severe enough for three patients to withdraw from treatment.

That the glycogen storage disorder underlies the LD PME was most strongly established when it was shown that simply reducing glycogen synthesis in the LD mouse models eliminates LBs and rescues the disease^{4,12-13}. Precisely how the LBs lead to epilepsy is unclear. Electron microscopy reveals that the cytoplasm of many if not most dendrites at synapses are occupied or replaced by LBs suggesting a possible impact on synaptic function¹⁴. One recent study suggested that there is preferential loss of GABAergic inhibitory interneurons¹⁵. Another reported that astrocytic glutamate clearance is impaired¹⁶, and there are yet other working hypotheses. In any case, perampanel would likely confer benefit by diminishing neuronal network hyper-excitability at least in part through its known AMPA antagonism.¹⁷ While the basic mechanisms of LD and its epilepsy are clarified and therapies directed against these root causes are developed, the present study supports the earlier more limited observations that perampanel is a beneficial new tool in this catastrophic epilepsy.

Acknowledgments

We would like to thank all the families affected by Lafora disease for participating in and supporting this work. BAM holds the University of Toronto Michael Bahen Chair in Epilepsy Research.

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Table 1
Methods Used to Determine Intensity of Myoclonus and Functional and Cognitive Impairment

1. Intensity of Myoclonus

- A.** Myoclonus frequency (0-5)
0, no myoclonus; 1, only part of the day; 2, less than every five minutes; 3, once every 3-5 minutes; 4, once every 1-2 minutes; 5, or more than once a minute
 - B.** Myoclonus severity (0-4)
 - C.** Amplitude of Myoclonus (0-3)
 - D.** Global assessment of intensity of myoclonus by patient caregiver (0-4)
- Adjusted Sum Score: $[(A+B+C+D)/16 * 10]$

2. Functional and Cognitive Impairment

- A.** Speech (0-4)
 - B.** Swallowing (0-4)
 - C.** Dressing/Hygiene/Use of Utensils (0-4)
 - D.** Walking/Balance (0-5)
 - E.** Presence of Falling (0-5)
 - F.** Alertness/Responsiveness (0-4)
 - G.** Global Assessment of Cognitive Performance/Level of Dementia (0-4)
- Adjusted Sum Score: $[(A+B+C+D+E+F+G)/30 * 10]$

Table 2
Demographics and Clinical Features of 10 Patients with Lafora Disease

Patient No.	Sex	Age	Country	Mutation	Duration of disease, y	Concomitant AED medications*	PER dose (mg/day)**	Adverse Events
1	F	21	USA	<i>EPM2A</i>	7.5	VPA, LEV, CLZ, ZNS, LZP, RFM,	9	
2	F	25	USA	<i>EPM2A</i>	14	VPA, LEV, CBZ, MDL, PIR	8	Increased GTCS
3	F	25	USA	<i>EPM2A</i>	10	RFM, VPA, LZP	8	
4	F	25	USA	<i>EPM2A</i>	8	VPA, LEV, ZNS, CLZ	6	Irritability, aggression, mood swings, trouble sleeping
5	M	20	England	<i>EPM2A</i>	4.5	VPA, LZP	4	Headaches
6	F	15	England	<i>EPM2A</i>	2	VPA, LEV, LZP, PIR	4	Loss of mobility, loss of coordination, cognitive slowing
7	F	18	Netherlands	<i>EPM2A</i>	4	PHB, VPA	10	Vision problems, increased GTCS
8	F	41	Sweden	<i>EPM2A</i>	27	PHB, CLZ, LEV, ZNS	4	Increased hallucinations
9	M	15	Turkey	<i>EPM2A</i>	6	LEV, VPA, CLZ	8	Nervousness, weakness, cognitive slowing
10	F	19	England	<i>EPM2B</i>	4.5	CLZ, LEV, VPA, PIR	4	Depressed mood

* VPA=Valproic Acid, LEV=Levetiracetam, CLZ=Clonazepam, CBZ=Clobazam, LZP=Lorazepam, RFM=Rufinamide, ZNS=Zonisamide, MDL=Midazolam, PIR=Piracetam, PHB=Phenobarbital

** Dosage of Perampanel (PER) at final evaluation

Table 3

Qualitative Analysis of Perampanel Efficacy in 7 Patients with Lafora Disease

Patient No.	No. of seizures/28 days ^b	Avg No. of seizures/28 days ^{2-3,9-10*} (% change)	Adjusted Myoclonus Score ^b	Adjusted Myoclonus Score ²⁻³	Adjusted Myoclonus Score ⁹⁻¹⁰	Functional Disability Score ^b	Functional Disability Score ²⁻³	Functional Disability Score ⁹⁻¹⁰
1	25	2.5 (90)	8.1	5.0	3.1	8.5	4.3	6.3
2	5	6 (-40)	6.6	5.0	5.0	7.0	7.0	7.7
3	10	5.5 (55)	9.4	7.2	7.5	10.0	9.7	9.7
4	9	0 (100)	5.0	2.5	2.5	4.7	5.7	5.7
5	1	0.5 (50)	6.9	6.9	6.9	9.0	9.3	9.3
7	1	1.5 (-150)	6.3	5.0	6.3	9.3	9.2	6.3
8	0	0 (0)	6.9	8.1	5.0	9.8	9.3	8.7
Average	6.0	2.3	7.0	5.7	5.2	8.3	7.8	7.7

* b=baseline, 2-3=2-3 months, 9-10=9-10 months