


Intravenous lacosamide for treatment of absence status epilepticus in genetic generalized epilepsy: A case report and review of literature

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Funding information

This work was supported by the State of Hesse with a LOEWE-Grant to the CePTER-Consortium.

Background: Nearly 10 years after its introduction into the market, the significance of lacosamide in genetic generalized epilepsies is still unclear. Its new mode of action may qualify lacosamide as a therapeutic agent in this entity, but only a limited number of cases have been published so far.

Aim: To describe the efficacy of lacosamide as treatment in a patient with the absence status epilepticus.

Method: We report on a 28-year-old woman with genetic generalized epilepsy who suffered recurrent absence status epilepticus during video-EEG-monitoring. After treatment failure of first- and second-line medication, lacosamide was administered. The outcome in this patient was evaluated, and a systematic literature review was performed for the use of lacosamide in the absence status epilepticus.

Results: After application of 400 mg lacosamide intravenously, the absence status epilepticus terminated within 30 minutes. No further seizures or epileptiform discharges reoccurred until the end of video-EEG-Monitoring 3 days later.

Conclusions: The role of lacosamide as a therapeutic option in patients with the absence status epilepticus is unclear. Only two cases have been reported so far with conflicting results. Further randomized controlled studies are required to validate the relevance of lacosamide as treatment for status epilepticus in genetic generalized and the absence epilepsy.

KEYWORDS

absence status epilepticus, genetic generalized epilepsy, lacosamide, levetiracetam, treatment failure

1 | INTRODUCTION

Since its introduction into the market in 2008, lacosamide (LCM) has become a well-established anticonvulsive medication for the treatment of focal onset seizures, with and without secondary generalization. Due to the availability of an intravenous formulation, its efficacy, tolerability, and lack of interaction potential, LCM is increasingly used with promising results as (off-label) second- or third-line therapy in patients with status epilepticus.¹ In contrast to focal epilepsies, little is known about the effect of LCM in genetic generalized epilepsies (GGE), but

pathophysiological considerations, supported by a limited number of case reports and uncontrolled trials, suggest a probable efficacy in that etiology.^{1,2} Here, we report a case of absence status epilepticus (ASE) in a patient with GGE terminated by a third-line treatment with LCM.

2 | CASE HISTORY

A 28-year-old woman with a history of epileptic seizures since the age of 17 was admitted to our video-EEG monitoring unit. She

had epilepsy of unknown etiology and reported frequent dialeptic and generalized seizures. Recurrent prolonged seizures and probable psychogenic non-epileptic seizures (PNES) were described previously. Previous MRI and EEG diagnostic failed to identify an epileptogenic focus or epileptiform discharges. No febrile seizures had occurred before, as confirmed by the mother and grandmother. A second degree relative with seizures during childhood was reported. Further details about the underlying epilepsy syndrome were not available. The initial medication with lamotrigine (LTG) up to 400 mg per day failed and additional treatment with levetiracetam (LEV) up to 1000 mg per day was tapered off after

manifestation of a depressive disorder. After discontinuation of LEV, add-on therapy with brivaracetam (BRV) up to 50 mg per day was initiated. Additional to the epileptic seizures, an anxiety disorder and arterial hypertension were described. The patient's physical examination was normal.

To record seizures during video-EEG-monitoring, BRV was immediately discontinued after admission. LTG was initially reduced to 50 mg twice per day and then stopped after 24 hours of a normal EEG recording.

In the second night, we observed generalized 2.5-3 Hz spike-wave complexes with steadily increasing frequency progressing into

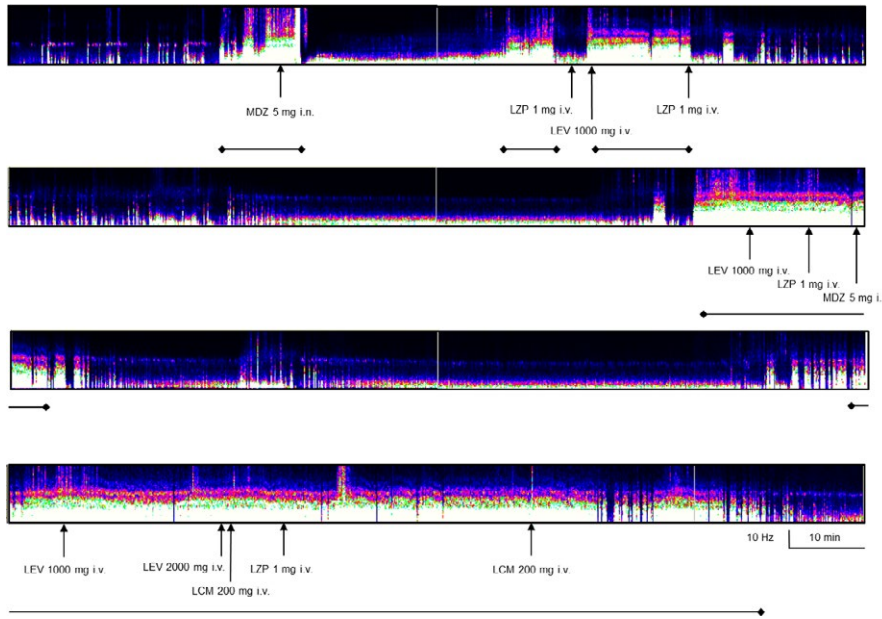


FIGURE 1 Spectral analysis of EEG during recurrent ASE and timepoint of administration of anticonvulsive medication

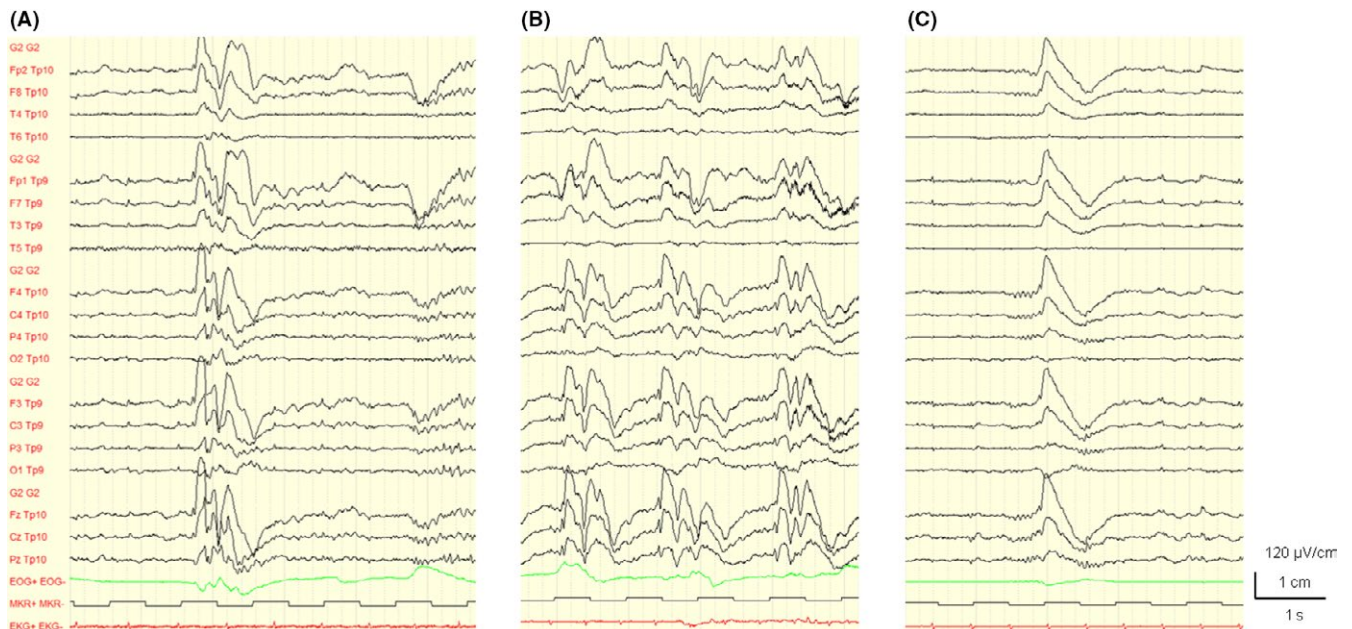


FIGURE 2 A, EEG with intermittent generalized spike-wave complexes, B, EEG seizure pattern during ASE, C, normal EEG after termination of ASE

prolonged absence seizures (see Figures 1 and 2). During a seizure series with a subsequent generalized tonic clonic seizure (GTCS) and a total duration of 11 minutes, 5 mg midazolam (MDZ) i.n. was subsequently dispensed. Lorazepam (LZP) was applied in a dosage of 1 mg between a second and third series. The third series lasted 15 minutes and terminated after application of 1000 mg LEV i.v. and 1 mg LZP i.v. The next ASE was recorded 130 minutes later and persisted over 33 minutes. This episode stopped after administration of 5 mg MDZ i.n., 1000 mg LEV i.v., and 1 mg LZP i.v. Another two hours later, ASE with ongoing generalized 3 Hz spike-wave complexes recurred. A 3000 mg LEV dosage, 200 mg LCM and 1 mg LZP were applied intravenously without any effect on seizure activity. A second dosage of 200 mg LCM was administered 40 minutes after the first application. Subsequent seizure activity resolved completely within the next half hour, 30 minutes after the last application of LCM, 65 minutes after the last application of LZP and 73 minutes after the last application of LEV. No additional seizures or epileptiform discharges were recorded until the end of the video-EEG-monitoring 3 days later. A 3T MRI was unremarkable without epileptogenic lesions. The patient history, seizure semiology, EEG, and imaging results suggest a GGE as underlying epilepsy syndrome. The patient was discharged 5 days after admission with well-controlled seizures on a combination therapy of 450 mg LTG and 200 mg BRV without side effects.

Ten weeks later, an ASE reoccurred and the patient was admitted again in our clinic. On continuous EEG ASE persisted despite application of 300 mg BRV i.v., 4 mg LZP i.v., and 1600 mg valproate i.v. We added 200 mg LCM i.v. twice and ASE resolved.

3 | DISCUSSION

The present case illustrates a potential therapeutic effect of LCM on ASE after treatment failure of first- and second-line therapy. The result was confirmed by EEG under controlled conditions in a video-EEG-monitoring unit.

To our knowledge, only two cases with ASE treated with LCM have been reported. Sodemann et al. reported successful treatment of ASE with 400 mg LCM i.v.³ In contrast to our case, no video-EEG-monitoring was performed and it was criticized that the observed clinical termination was two hours after application of LCM, and therefore, a spontaneous termination unrelated to LCM was more likely.⁴ In another patient with ASE and only transient effect of benzodiazepines, LCM was administered with 200 mg twice within 10 minutes. No effect on EEG was found and ASE regressed spontaneously after 24 hours.⁵

In our case, seizures resolved during the first four episodes under medication with benzodiazepines and/or LEV. These medications seemed to be insufficient during the last status episode, which lasted for 120 minutes. Pharmacokinetic studies showed that LEV, LZP, and LCM rapidly reach the maximum plasma concentration after intravenous administration.⁶⁻⁸ LCM and LZP cross the blood-brain barrier regularly within a few minutes. In contrast, maximum concentrations of LEV in the extracellular brain tissue

occur with a significant time gap to the administration. Maximum levels were found more than one hour after peak plasma concentrations.⁸ In our case, LEV was applied 96 and 73, LZP 65, and LCM 70 and 30 minutes before the seizure stopped. A delayed effect of LEV cannot be completely ruled out, but the last ASE stopped ultimately only after administration of LCM. The patient was discharged under a medication with LTG and BRV. This medication was initiated 10 hours after the termination of ASE. As consequence, no long-term effects of LCM can be judged. In any case, there was no indication of any negative effect of LCM on ASE control.

In absence epilepsy, both activation of t-type calcium channels in the thalamocortical circuit and a decrease in GABA(A) inhibition were mentioned as underlying pathophysiological conditions.^{9,10} However, LCM is not known to have an effect on t-type calcium channels or GABA(A) receptors. Compared to other sodium channel blockers, LCM possesses a new mechanism causing an enhanced slow inhibition of voltage gated sodium channels without effect on fast channel inactivation, as known for the sodium channel blockers lamotrigine, carbamazepine, or phenytoin.⁹ In an animal model for generalized epilepsy using an intravenous infusion of the GABA(A)-receptor blocking agent pentylenetetrazol (PTZ), an elevation of seizure threshold after application of LCM was found. Interestingly, this effect was not observed in the same model after s.c. application of PTZ. However, in both cases, no proconvulsive effects by LCM were reported.² Unpublished data were mentioned by Wechsler et al. suggesting worsening of epileptiform activity in a genetic mouse model for the absence seizures after application of LCM.¹¹ The absence epilepsy usually follows complex inheritance where the interaction of multiple gene variants and environmental factors is responsible for the development of epilepsy. There is considerable genetic variability between different affected individuals, which may relate to variability in treatment effects as well.¹²

An aggravation of seizures in IGE patients due to anticonvulsive drugs is a well-known phenomenon and established especially for the use of CBZ.¹³ Abarategui et al. reported two patients with juvenile absence epilepsy without ASE and aggravated seizures under LCM.¹⁴ Also in other conditions as Lennox-Gastaut syndrome a worsening of seizures were observed in some patients.¹⁵ Additional, an induction of negative myoclonus during a combined treatment with CBZ and LCM was found in one case with focal epilepsy.¹⁶ For GGE with primary generalized seizures, some rare, underpowered, and uncontrolled trials suggest a therapeutic effect of LCM, but the evidence is weak compared to the situation in patients with focal seizures.^{1,11,14,17}

4 | CONCLUSION

The role of LCM as an anticonvulsant in patients with ASE is unclear. The literature provides conflicting data with low evidence for efficacy in GGE. In patients with contraindications against established medications, such as valproate or levetiracetam, or where

these medications have failed, the intravenous formulation of LCM may have the potential to become a therapeutic option in the future. Randomized controlled studies are necessary to validate the relevance of LCM for treatment in status epilepticus in GGE and the absence epilepsy.

ACKNOWLEDGEMENTS

We are grateful to all of our video-EEG-monitoring technicians for their assistance.

CONFLICTS OF INTEREST

COI are stated following the guidelines of the International Journal of Clinical Practice (Graf et al. 2007, Best Practice Guidelines on Publication Ethics: a Publisher's Perspective, Int J Clin Pract, 2007;61(152);1-26). P. S. Reif, A. Männer, L. Kay and J. P. Zöllner report no conflicts of interest. L. M. Willems reports travel grants by Eisai. K. M. Klein reports grants and fees by UCB Pharma, Eisai und Novartis. F. Rosenow reports personal fees from Eisai, grants and personal fees from UCB Pharma, grants and personal fees from Desitin Arzneimittel, grants and personal fees from GW pharma personal fees and other from Novartis, personal fees from Medtronic, personal fees from cerbomed, personal fees from Shire, personal fees from the vfa, grants from European Union, and grants from Deutsche Forschungsgemeinschaft. A. Strzelczyk reports personal fees and grants from Desitin Arzneimittel, Eisai, LivaNova, Sage Therapeutics, UCB Pharma, and Zogenix. 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.

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How to cite this article: Reif PS, Männer A, Willems LM, et al. Intravenous lacosamide for treatment of absence status epilepticus in genetic generalized epilepsy: A case report and review of literature. *Acta Neurol Scand*. 2018;00:1-4. <https://doi.org/10.1111/ane.12935>