CASE REPORT

Status epilepticus developing during lacosamide monotherapy

Savvas S Papacostas

Neurology Clinic B and School of Molecular Medicine, Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

Correspondence to
Professor Savvas S Papacostas,
savvas@cing.ac.cy

Accepted 9 January 2015

SUMMARY

Two cases with partial onset epilepsy who developed status epilepticus (SE) on lacosamide (LCM) monotherapy are reported. LCM is an effective adjunctive antiepileptic drug (AED) for partial-onset epilepsy and as infusion in SE. It has also shown efficacy in monotherapy. The reported cases achieved control of seizures with adjunctive LCM treatment and were afterwards converted to monotherapy. Both patients subsequently developed SE while on LCM monotherapy. They were on monotherapy for at least 2 months after withdrawal of concomitant AEDs precluding the possibility of withdrawal-induced SE. Pharmacovigilance is indicated when LCM is administered in monotherapy in order to assess its proper therapeutic potential and its putative limitations especially in cases where it may prove ineffective. Moreover, vigilance is necessary whenever any concomitant antiepileptic is tapered regardless of the substances used. Higher doses may be needed when an AED is used in monotherapy.

BACKGROUND

Lacosamide (LCM), a novel antiepileptic drug (AED), consists of a functionalised amino acid molecule that stabilises hyperexcitable neuronal membranes and inhibits repetitive firing.¹ It acts on slow sodium channels to prolong hyperpolarisation without affecting fast inactivation.² It has efficacy when added to concomitant AEDs,³ and is recommended as adjunctive therapy in partial-onset seizures with or without secondary generalisation. Moreover, it may be effective in primary generalised epilepsy as monotherapy or adjunctive treatment.^{4, 5} It is available for intravenous infusion in bioequivalence to the oral formulation,⁶ and is emerging as a second-line agent against status epilepticus (SE). The pharmacokinetic and safety profile of LCM has been recently reviewed;^{2, 6} it includes linear kinetics, complete bioavailability and no major drug interactions.⁶ Common side effects following infusion include headache, dizziness, diplopia and somnolence, and are dose-dependent.² In a retrospective study on hospitalised patients, 9.4% developed adverse events: one case had altered mental state and prolonged PR interval on ECG; one had unexplained thrombocytopenia; and another reported dizziness; all of these resolved after drug discontinuation.⁷

The efficacy of LCM in monotherapy has been demonstrated in a large phase III trial,⁸ however, extensive worldwide experience is still lacking. Two cases are presented, in which the patients

developed SE on LCM monotherapy following withdrawal of concomitant AEDs.

CASE PRESENTATION**Case 1**

A 33-year-old right-handed man was involved in a road traffic accident at age 19 and sustained closed head trauma with subsequent development of a haematoma requiring evacuation. Thereafter he developed hydrocephaly and partial epilepsy with secondary generalisation. His medical history was unremarkable. He denied smoking, illicit drug or alcohol abuse. Clinically he had mild dysarthria, saccadic eye pursuits to the left, right-sided spastic hemiparesis and left-sided lower extremity spasticity. He was on carbamazepine (CBZ) 800 mg daily, baclofen 40 mg daily and diclofenac 75 mg *pro re nata* (when necessary) for headaches. MRI of the brain revealed a well-placed and functioning shunt, and a left hemispheric porencephaly with gliosis in the frontal, parietal and temporal lobes, and basal ganglia; there was also gliosis over the right frontal lobe and centrum semiovale. EEG revealed the presence of diffuse background slowing and disorganisation, and continuous δ waves over the left hemisphere admixed with multifocal epileptiform activity. Seizures were not adequately controlled and CBZ was titrated to 1200 mg daily. Botulinum toxin injections were administered for spasticity. Because of side effects the patient's CBZ dose was decreased, however, this caused an exacerbation of seizures. He was augmented with topiramate (TPR) titrated to 400 mg daily. He experienced seven seizures over the following 4 months and a rash, which was TPR-related according to a dermatologist. LCM was added next and titrated to a dose of 400 mg daily whereas TPR was withdrawn. The patient remained seizure-free for the next 1 year at which point CBZ was gradually withdrawn in order to improve his cognitive status. Two months later, he presented to the emergency department in convulsive SE, which was controlled with two 5 mg boluses of diazepam and 1000 mg phenytoin (PTH), intravenously. The episode lasted about 90 min from its onset until medical care was given. No residual deficits were noted. Provocative factors were not identified and compliance was ascertained by his family members, who administered his medications. Thereafter he was maintained on a combination of LCM 400 mg and oxcarbazepine (OXC) 1200 mg daily.

Case 2

A 56-year-old man presented with partial epilepsy following an aneurysmal rupture. He had a residual

CrossMark

To cite: Papacostas SS. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206354

right hemiparesis, dysarthria and severe cognitive impairment. He had seizures about every 2 months. His medical history was significant for hypertension, hypercholesterolaemia and mild chronic renal failure. Medications included PTH 300 mg daily, amlodipine 5 mg daily, carvedilol 6.25 mg daily, ramipril 5 mg twice daily, hydrochlorothiazide 25 mg daily, OXC 900 mg daily, simvastatin 20 mg daily and omeprazole 40 mg daily. CT of the brain revealed ventricular enlargement especially over the left temporal horn and a hypodense lesion in the left parietal lobe consistent with an ischaemic infarct. EEG revealed continuous left temporoparietal δ slowing with occasional sharp waves. OXC was titrated to 1200 mg daily. The patient subsequently reported two-to-three seizures daily consisting of right-sided hemiconvulsions evolving to generalised tonic-clonic. Titration of OXC to 1800 mg daily caused dizziness and somnolence. LCM was added and titrated to 400 mg daily. Four months later, on a follow-up visit, he reported that his seizures had resolved. Inadvertently, however, he had discontinued OXC but maintained LCM monotherapy and reported feeling more alert. Two months later, he had an episode of focal SE aborted by diazepam 5 mg and PHT 1000 mg intravenously. He was restarted on OXC 1200 mg daily in addition to PHT 300 mg daily and LCM.

OUTCOME AND FOLLOW-UP

Both cases have been maintained on combination antiepileptic therapy; the first case on LCM and OXC and the second on LCM, PTH and OXC. They have remained seizure-free for 14 and 8 months, respectively. They will be maintained on combination therapy with LCM with one or two concomitant AEDs as needed.

DISCUSSION

The cases presented developed SE following conversion to LCM monotherapy. To our knowledge, this is the first report in the English literature of SE developing on LCM monotherapy. It is unlikely that LCM was the cause of SE, because it attained a score of 3 on the Naranjo adverse reaction probability scale,⁹ and since other AEDs such as OXC and eslicarbazepine, which are effective in monotherapy, act through a similar mechanism.¹⁰ However, this occurrence may suggest that LCM is more effective when combined with other AEDs, namely OXC, or that, possibly, somewhat higher doses are required in monotherapy, although in a retrospective analysis⁸ of conversion to monotherapy a dose of 400 mg daily was effective, with a favourable safety profile in patients with focal epilepsy, whereas the predicted exit percentage (32.3%; 95% CI 26.8% to 37.8%) was lower (30.0%; 95% CI 24.6% to 35.5%) than the historical control. Both patients had been on LCM monotherapy for 2 months, precluding the possibility that SE developed due to concomitant AED withdrawal in close proximity to the event; this highlights the fact that tapering one substance in a combination therapy may result in seizure deterioration, independent of the AEDs used.

In a post hoc analysis, adjunctive LCM demonstrated significant seizure reduction over placebo regardless of the inclusion of 'traditional' sodium channel blocking concomitant AEDs.¹¹ The potential for additive and/or synergistic effects in combination

with non-sodium channel blocking AEDs may also prove useful.¹² In another study, patients taking traditional sodium blockers were as likely to become seizure-free as those taking AEDs with other mechanisms of action,¹³ and two achieved monotherapy status.

LCM efficacy, however, may depend on synergism with other AEDs in addition to its unique mechanism. Therefore, further studies and vigilant monitoring are needed to clarify its therapeutic role on different types of seizures as monotherapy and as adjunctive treatment.

Learning points

- ▶ Lacosamide (LCM) is an effective adjunctive antiepileptic in partial-onset epilepsy.
- ▶ It is emerging as effective abortive therapy for status epilepticus.
- ▶ It has promising potential as monotherapy in focal-onset epilepsy.
- ▶ A higher dose of LCM may be needed in monotherapy.
- ▶ Vigilant monitoring is needed for patients who may not respond favourably to monotherapy and may actually have exacerbation of seizures or status epilepticus.

Acknowledgements Special thanks to Mrs Elena Polycarpou and Mrs Christina Hadjiyianni for their technical assistance.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Doty P, Rudd GD, Stoehr T, *et al*. Lacosamide. *Neurotherapeutics* 2007;4:145–8.
- 2 Hoffer J, Trinka E. Lacosamide as a new treatment option in status epilepticus. *Epilepsia* 2013;54:393–404.
- 3 Sawh SC, Newman JJ, Deshpande S, *et al*. Lacosamide adjunctive therapy for partial-onset seizures: a meta-analysis. *Peer J* 2013;1:e114.
- 4 Zangaladze A, Skidmore C. Lacosamide use in refractory idiopathic primary generalized epilepsy. *Epilepsy Behav* 2012;23:79–80.
- 5 Afra P, Adamolekun B. Lacosamide treatment of juvenile myoclonic epilepsy. *Seizure* 2012;21:202–4.
- 6 Biton V. Lacosamide for the treatment of partial-onset seizures. *Expert Rev Neurother* 2012;12:645–55.
- 7 Luk ME, Tatum WO, Patel AV, *et al*. The safety of lacosamide for treatment of seizures and seizure prophylaxis in adult hospitalized patients. *Neurohospitalist* 2012;2:77–81.
- 8 Wechsler RT, Li G, French J, *et al*. Conversion to lacosamide monotherapy in the treatment of focal epilepsy: results from a historical-controlled, multicenter, double-blind study. *Epilepsia* 2014;55:1088–98.
- 9 Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
- 10 Soares-da-Silva P, Hebeisen S. Slow and fast inactivator of voltage gated sodium channels by eslicarbazepine and carbamazepine. *Epilepsia* 2012;53(Suppl.5):54.
- 11 Sake JK, Hebert D, Isojarvi J, *et al*. A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. *CNS Drugs* 2010;24:1055–68.
- 12 Shandra A, Shandra P, Kaschenko O, *et al*. Synergism of lacosamide with established antiepileptic drugs in the 6-Hz seizure model in mice. *Epilepsia* 2013;54:1167–75.
- 13 Stephen LJ, Kelly K, Parker P, *et al*. Adjunctive lacosamide in clinical practice: sodium blockade with a difference? *Epilepsy Behav* 2011;22:499–504.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow