Original article

Epileptic Disord 2020; 22 (1): 83-9

Cardioembolic acute cerebral micro-infarcts in the context of atrial fibrillation after low-dose intravenous infusion of lacosamide

Álvaro Beltrán Corbellini, Paula Pérez Torre, Velina Nedkova Hristova, Beatriz Zarza Sanz, Adriana Celdrán de Castro García, Fernando Rodriguez Jorge, Juan Luís Chico García, Paloma Parra Díaz, Francisco Javier Buisan Catevilla

Department of Neurology, Hospital Universitario Ramón y Cajal. Madrid, Spain

Received May 16, 2019; Accepted December 04, 2019

ABSTRACT – *Aims*. Lacosamide (LCM) is a well-tolerated and increasingly used second-generation AED, and side effects such as atrial fibrillation are rare and poorly characterized. Supported by a literature review, we share our experience of the management of the first reported case of cardioembolic cerebral infarcts in the context of *de novo* atrial fibrillation, which appeared following a 200-mg intravenous infusion of LCM for the treatment of non-convulsive status epilepticus.

Methods. Case report and literature review using search items including "atrial fibrillation OR atrial flutter AND LCM" in the thesaurus of Medline.

Results. We found three cases of atrial fibrillation/atrial flutter secondary to LCM, one following a 200-mg intravenous infusion. In one patient, previous risk factors for atrial fibrillation were reported and another was started on warfarin; all required suspension of LCM for cessation of atrial fibrillation. Previous risk factors for atrial fibrillation in our patient were older age, male gender, obesity, hypertension, valvular disease, first-degree atrioventricular block and left anterior fascicle block. Atrial fibrillation appeared at the end of the infusion and ceased after a loading dose of amiodarone and suspension of LCM. Apixaban was initiated indefinitely five days later, and MRI showed four acute silent infarctions.

Conclusions. The appearance of atrial fibrillation has severe therapeutic and clinical implications and the use of LCM might be reconsidered within a context of increased predisposition to developing atrial fibrillation. If atrial fibrillation appears, the drug should be discontinued and anticoagulation should be considered according to embolic risk. Further investigation is needed in order to better categorize the risk profile of lacosamide regarding atrial fibrillation.

Key words: status epilepticus, lacosamide, arrhythmia, atrial fibrillation, stroke, elderly

Correspondence:
Álvaro Beltrán Corbellini
Secretaría de Neurología,
Hospital Universitario Ramón y Cajal,
Crta,
Colmenar, Km 9, N° 100. Madrid, Spain
<beltran_corbellini@hotmail.com>

doi:10.1684/epd.2020.1136

Lacosamide (LCM) is a second-generation antiepileptic drug (AED) approved for monotherapy or adjuvant therapy for focal onset seizures with or without secondary generalization in adults, adolescents and children older than four years of age with epilepsy (UCB Pharma, 2019). Its mechanism of action consists of specific enhancement of slow inactivation of voltage-gated sodium channels with stabilization of neuronal membranes, as well as inhibition of the collapsin response mediator protein 2 (CRMP-2), which is thought to mediate neurite outgrowth and contribute to epileptogenesis (Rogawski *et al*., 2015; Wang *et al*., 2018).

Regarding cardiac arrhythmias as adverse events related to LCM, dose-dependent PR interval prolongation, atrioventricular blocks and bradycardia were described for both oral and intravenous routes of administration in the three randomized controlled trials which first led to the approval of LCM (Ben-Menachem *et al*., 2007; Halasz *et al*., 2009; Chung *et al*., 2010) in the post-marketing setting as the main observed arrhythmic events (Shaibani *et al*., 2009; Wymer *et al*., 2009; Krause *et al*., 2011; Nizam *et al*., 2011). Thus, some current clinical practice guidelines assume second and third-degree atrioventricular block as the unique contraindications for the use of LCM (Mercadé Cerdá *et al*., 2016).

Other arrhythmic events have been described much less frequently in relation to the administration of LCM. To our knowledge, two well-documented cases of atrial flutter/atrial fibrillation (AF) have been reported to date, concerning different dosages and routes of administration (DeGiorgio, 2010; Kaufman *et al*., 2013).

In this paper, we report the first case of cardioembolic cerebral infarcts within the context of *de novo* AF which appeared following a low-dose intravenous infusion of LCM for the treatment of non-convulsive status epilepticus. As well as the clinical experience of this case, we discuss a literature review and bring to the forefront the circumstances in which AF may arise, following administration of LCM in the presented and precedent case reports. Possible risk factors for AF are considered related to the usage of LCM in order to better categorize the associated risk profile.

Materials and methods

We report a case of cardioembolic cerebral infarcts within a context of *de novo* AF which appeared following intravenous infusion of LCM for the treatment of non-convulsive status epilepticus. Moreover, a literature review is described using the terms "lacosamide" AND "atrial fibrillation OR atrial flutter" in the thesaurus of Medline.

Case report

An 88-year-old, right-handed man was referred to the emergency department because of confusion. He had a history of obesity, hypertension, hypercholesterolaemia and mild aortic and mitral insufficiencies with type I diastolic failure (based on a transthoracic echocardiogram a year ago, also showing a normal left atrium). He had also presented, within the last 15 years, with several episodes consisting of behavioural arrest, loss of awareness of the environment, and staring with subsequent repetitive language and reiterative questions lasting for 20 minutes, with post-episodic amnesia. The latter was interpreted by his general practitioner as episodes of transient global amnesia, and the patient was initiated on clopidogrel at 75 mg/24 hours. Moreover, he was also on ramipril, simvastatin, acetaminophen and pantoprazol.

His wife stated that she had found him in the street disoriented in space and time, with limited and unintelligible speech and a lost gaze.

At first evaluation, he presented with arterial pressure of 165/95 mmHg, rhythmic at 85 bpm, afebrile, and with capillary blood glucose of 95 mg/dL. He manifested considerable psycho-motor agitation, inattention and moderate mixed aphasia with a tendency for repetitive language with no other symptoms or signs.

An EKG showed sinus rhythm at 66 bpm, first-degree atrioventricular block (0.24 s) and left anterior fascicle block (LAFB). Blood test showed sodium at 133 mEq/l, leukocytes at 18,500/mm^3 and neutrophils at 15,900/mm^3, with CRP at 1.7. Simple cranial CT, cranial perfusion CT and cranial angio-CT showed no remarkable signs. A very distorted EEG showed left temporal intermittent slowing with global low voltage and slow activity.

Therefore, suspecting non-convulsive status epilepticus during EEG registration, the patient was started on LCM at 200 mg via a 20-minute intravenous infusion. After 15 minutes from the onset of the infusion, the EKG monitoring showed frequency-dependent AF with rapid ventricular response (140 bpm). LCM infusion was suspended without clinical or EEG improvement, and after cardiological assessment, the patient was started on a loading dose of amiodarone at 300 mg intravenously. Forty minutes after, ECG monitoring showed reversion to sinus rhythm, and amiodarone was reduced to 900 mg/24 hours intravenously and then 200 mg/8 hours orally. Since this was an AF episode with high embolic risk (CHA2DS2-VASc 3), the next day, the patient started anticoagulant therapy with apixaban at 5 mg/12 hours indefinitely.

Valproic acid (VPA) at 2 g as intravenous infusion was started and the patient was admitted in the stroke unit for monitoring. He continued manifesting considerable psycho-motor agitation and moderate mixed

aphasia with a tendency for repetitive language. Clonazepam at 0.5 mg, as a 24-hour continuous intravenous infusion, was finally started, and after 90 minutes from the onset of the infusion, clinical improvement was observed and a clinical basal level was achieved the following morning. He was now asymptomatic.

VPA infusion was reduced to 1,500 mg/24 hours and clonazepam infusion was suspended. Six hours later, the patient manifested with another episode consisting of disorientation and mixed aphasia, which spontaneously finished within a few minutes. An EEG registered two hours after the episode showed predominant right fronto-temporal rhythmic and intermittent delta activity with mild and diffuse slowing. Levetiracetam (LEV) at 500 mg/12 hours was added to VPA at 500 mg/12 hours.

During the following four days of hospitalization, the patient presented with no other episodes suggestive of an epileptic origin, neurological focal manifestations, or other arrhythmic events.

Cranial MRI performed five days after the episode of AF showed four spot-shaped foci of restricted diffusion on diffusion-weighted images, localized to deep white matter adjacent to the left lateral ventricle body, left parietal cortex, superior cerebellar vermis and right occipital lobe, suggesting asymptomatic cardioembolic acute micro-infarcts (*figure 1*).

The patient was discharged with LEV at 500 mg/12 hours, VPA at 500 mg/12 hours, amiodarone at 200 mg/8 hours and apixaban at 5 mg/12 hours, with an unremarkable physical examination.

Results and discussion

Based on a literature review and to the best of our knowledge, there are just two well-documented case reports of AF which were thought to be secondary to LCM. Additionally, in a phase III double-blinded randomized placebo-controlled trial evaluating the efficacy and safety of different dosages of oral LCM in patients with painful diabetic neuropathy (Shaibani *et al*., 2009), two patients in the 600-mg/day group (1,5 %) developed AF, considered by the investigator to be possibly related to trial medication. There are no available data regarding the individual features of these patients, such as possible proarrhythmic risk factors or specific characteristics of the AF episode, including anticoagulation. Both events resolved.

There is also one case report of a 37-year-old woman with severe intractable focal seizures with loss of awareness who developed atrial flutter while on oral LCM at 600 mg/day and lamotrigine (LTG) at 300 mg/day (DeGiorgio, 2010). The patient was already on LTG at 300 mg/day and LCM was slowly titrated over several weeks to 600 mg/day. She developed atrial flutter with rapid ventricular response after weeks on oral LCM at 600 mg/day. At that time, she was started on warfarin, and LCM was reduced to 400 mg/day. Two weeks later, atrial flutter persisted and so LCM was reduced at a rate of 100 mg/week. One week after discontinuation of LCM, atrial flutter resolved and warfarin was discontinued. Atrial flutter did not present again during follow-up. No known risk factors for AF/flutter were present.

The last case report consists of a 67-year-old woman who developed AF with rapid ventricular response at the end of a low-dose (200-mg) intravenous infusion of LCM over 60 minutes within the context of complex partial status epilepticus (Kaufman *et al*., 2013). LCM was discontinued following the infusion, and AF spontaneously resolved within eight hours. After 96 hours from the initial AF, it reappeared and was self-limiting within minutes, without any clinical

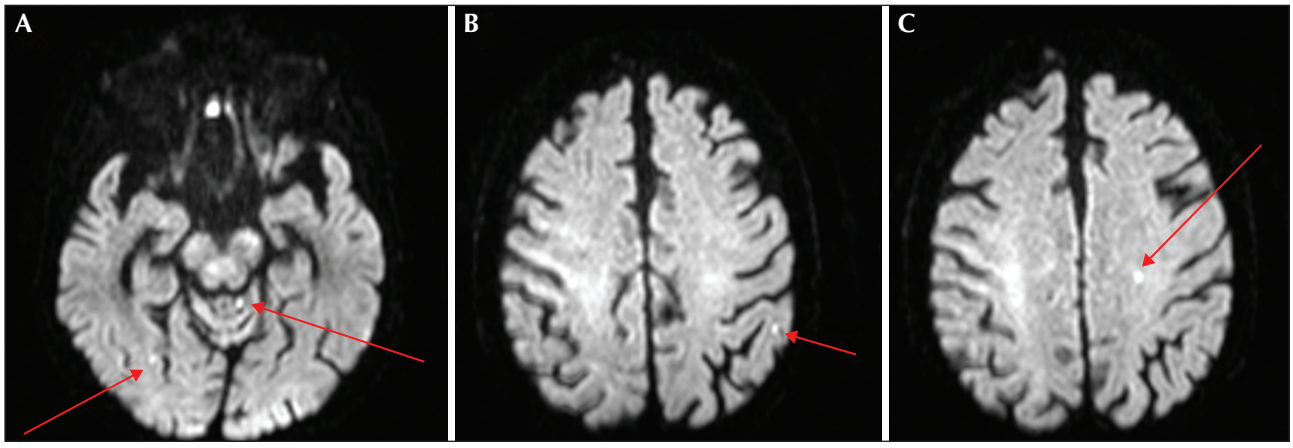

Figure 1. MRI showing spot-shaped foci of restricted diffusion on diffusion-weighted imaging (DWI) sequences localised to the superior cerebellar vermis and right occipital lobe (A), left parietal cortex (B), and deep white matter adjacent to the body of the left lateral ventricle (C).

complication. No anticoagulant therapy was started. In this case, investigators reported older age, possible cardiac amyloidosis and parental AF as risk factors for the AF condition.

In summary, of the two typified cases of AF, one appeared with supramaximal off-label dosages of oral LCM (600 mg/day) and the other after a 200-mg IV infusion over 60 minutes. In both cases, AF disappeared after discontinuation of LCM with no necessity for antiarrhythmic drugs. In one case, warfarin was started and then discontinued when AF disappeared. None of the episodes were associated with clinical complications.

Before the discussion regarding LCM and AF in our patient, we provide a brief analysis of the rationale for the management of clinical suspicion of non-convulsive status epilepticus and selection of first-line AEDs in this case.

Since a normal multimodal CT scan had ruled out a stroke, and given the medical history of the patient (suggestive of epilepsy with focal seizures with impaired awareness), the next immediately modifiable condition to be considered in the emergency setting was non-convulsive status epilepticus. Clinical manifestations could suggest an epileptic origin and although the initial EEG (interpreted as left temporal intermittent slowing added to global low-voltage, slow activity) did not match the modified Salzburg consensus criteria for non-convulsive status epilepticus (Leitinger *et al*., 2015), it was very distorted and hardly analysable due to the severe psycho-motor agitation of the patient.

For this reason, we decided to test clinical and EEG reactivity to an intravenous AED. As first-line therapy, it was decided not to start the patient on phenytoin (PHT) or VPA because of their increased propensity for adverse effects in the elderly (Nanau and Neuman, 2013; Guldiken *et al*., 2016; Abou-Khalil, 2016). Since LEV could have worsened the severe psycho-motor agitation and hostility the patient was showing (Abou-Khalil, 2016; Hansen *et al*., 2018), it was also not administered as first-line therapy. Hence, we decided to administer LCM, a drug which is becoming more popular as treatment for status epilepticus given its global favourable safety and tolerability profiles and promising efficacy results (Strzelczyk *et al*., 2017).

The delay in the diagnosis of epilepsy in our patient (of up to 15 years) also deserves mention. The incidence of epilepsy in people over 80 is three-fold greater than that in children, and in the elderly, a diagnosis is challenging and requires a high index of suspicion since the clinical presentation of seizures in this population is different from that in younger age groups. A concomitant presentation of cognitive impairment may exist, however, the findings based on routine tests are non-specific since this may be confused with several entities (*e.g*. syncope, transient ischaemic attack or, in our case, transient global amnesia) (Ghosh and Jehi, 2014). Overall, all of these factors could lead to a delay in the diagnosis and in turn to a delay in the onset of therapy, worsening the prognosis, as the case of our patient illustrates.

Furthermore, it is known that cardiac comorbidity is frequent among patients with epilepsy (Shmuely *et al*., 2017). Regarding the various mechanisms that may account for this co-existence, several cardiac arrhythmias such as AF have been reported to result from seizure activity. In this context, a few case reports of seizure-related AF episodes have been described, most of them in the post-ictal setting after convulsive seizures (Van der Lende *et al*., 2016). However, to our knowledge, no episodes of AF have been reported concerning the ictal or post-ictal phases of non-convulsive status epilepticus. The underlying pathophysiological background of AF within the context of convulsive seizures could be related to a rise in catecholamine level and an increased sympathetic tone (Sturges *et al*., 2012).

The risk factors for AF in our patient are well known and included older age, male gender, obesity, hypertension and valvular disease (Benjamin *et al*., 1994). First-degree atrioventricular block in hypertensive patients (Uhm *et al*., 2014; Lehtonen *et al*., 2018) and LAFB (Nguyen *et al*., 2016) have also been demonstrated as independent risk factors for AF.

AF arose at the end of administration of the intravenous loading dose of LCM, coinciding with the maximum theoretical serum concentration of the drug (Fountain *et al*., 2013), thus making arrhythmic adverse reactions more probable in a patient with proarrhythmic risk factors. This argument has already been used in a previous case report of AF at the end of low-dose LCM intravenous infusion (Kaufman *et al*., 2013). Moreover, according to the Naranjo's Adverse Reaction Probability Scale, the appearance of AF due to prior administration of LCM in this case was classified as probable (scoring 6 points) (Naranjo *et al*., 1981). Given these facts, cardiological investigation also led to the conclusion that AF was secondary to the administration of LCM within this context.

In the context of AF, the pathophysiology and risk-modifying factors of thrombus formation are not yet fully understood. However, several variables such as particular morphological parameters of the left atrium or duration of AF episodes have been reported to modify the risk of thrombus formation and brain embolism. Concerning the duration of AF episodes and stroke risk, it has been demonstrated that a single AF episode with a high rate lasting for more than five minutes (our patient manifested a 40-minute AF episode) significantly increases the risk of stroke. In fact, most studies in this field consider 5-6 minutes as the threshold for a

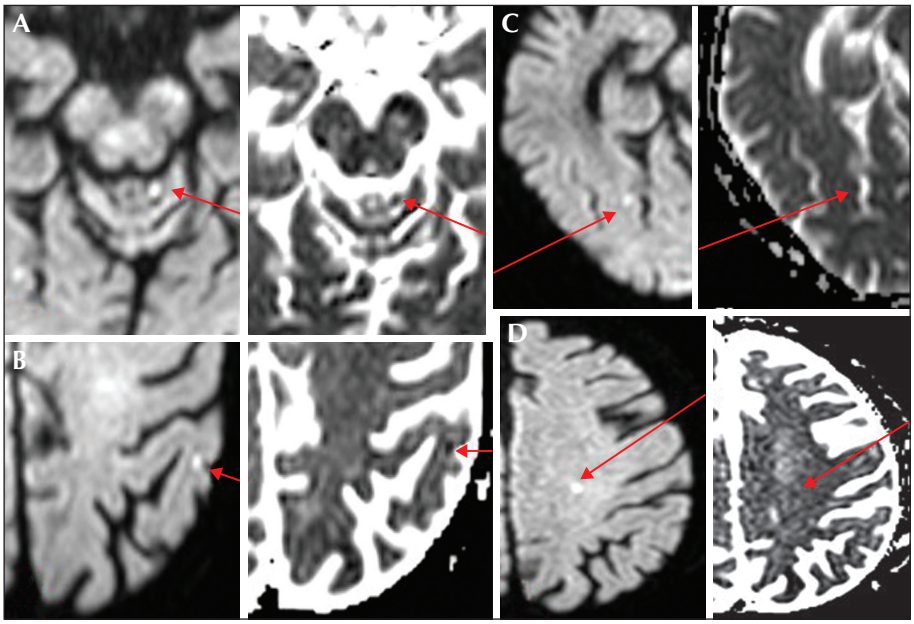

Figure 2. MRI showing spot-shaped restriction foci of restricted diffusion on DWI and their corresponding hypointensity on ADC maps localised to the superior cerebellar vermis (A), left parietal cortex (B), right occipital lobe (C), and deep white matter adjacent to the body of the left lateral ventricle (D), suggestive of acute cerebral micro-infarcts.

significant increment in thromboembolic risk and an assessment of the need for anticoagulation (for review see Glotzer and Ziegler, 2013).

According to the Causative Classification System for Ischemic Stroke (Ay *et al.*, 2007), the cardioembolic aetiology of the silent infarctions observed on the MRI diffusion-weighted images (DWI) of our patient was classified as "evident". In addition, morphological features of the infarctions were consistent with a cardioembolic aetiology, and regarding the timing, DWI and apparent diffusion coefficient (ADC) images (*figure 2*) suggested that infarctions had evolved over up to five days (Schlaug *et al.*, 1997) (cranial MRI was performed five days after the episode of AF).

The appearance of AF within the context of LCM infusion had important clinical and therapeutic implications for our patient, such as the initiation of amiodarone. Moreover, given the high embolic and bleeding risk (pre-infarcts CHA_2DS_2-VASc with 3 points [age 75 years or older, 2 points; hypertension, 1 point] and HAS-BLED with 3 points), initiation of oral anticoagulation (with apixaban, in the case of our patient) should be considered according to the European Society of Cardiology guidelines for the management of AF, and male patients with a CHA_2-DS_2-VASc score of 1 or more are likely to benefit from oral anticoagulation during primary prevention of stroke (Kirchhof *et al.*, 2016). These drugs are not risk-free and could eventually give rise to severe adverse reactions such as major haemorrhaging. Ultimately, cerebral infarcts were objectified, which is the most severe complication of AF.

Given the reported case and literature review, and since the appearance of AF may lead to severe clinical complications and changes in management that are not risk-free, the global risk for developing AF should be assessed before administering LCM, whatever the route or clinical setting. Moreover, warnings regarding other arrhythmic conditions reflected in the LCM technical datasheet (UCB Pharma, 2019) should be taken into account. Thus, a 12-lead EKG should be obtained before starting treatment with LCM in order to assess contraindications as well as the risk profile associated with other less frequent adverse reactions such as AF. This recommendation goes along the same lines as that in the LCM technical datasheet (UCB Pharma, 2019). LCM is an effective and well-tolerated AED with a good pharmacokinetic profile, but in high-risk situations, therapeutic alternatives exist and may be considered.

In our opinion, the main reasons for not recommending ECG monitoring during and after IV LCM infusion regarding the risk of AF are the low number of reported cases of AF thought to be secondary to LCM and the fact that, with such little evidence, the lack of logistic capacity for ECG monitoring in many centres would probably prevent a large number of patients benefitting from LCM infusion within the context of status epilepticus.

On the other hand, in the context of status epilepticus and the high level of predisposition to developing

severe arrhythmic events (such as AF), as well as no other available therapy, we suggest infusion of LCM at 200 mg via administration of a 60-minute loading dose instead of a 30-minute or less infusion of 300-400 mg. The rationale for this suggestion is based on an open label trial which demonstrated that adverse reactions are greater with the 400-mg loading dose than with the 200-300-mg loading dose (Fountain *et al*., 2013). This trial employed a 15-minute loading dose regimen, and as mentioned in the LCM technical datasheet (UCB Pharma, 2019), adverse reactions that occurred one week after the infusion were similar in frequency to those that occurred over a three-month period of adjunctive therapy in controlled trials, indicating that the incidence of adverse reactions could be higher with the 15-minute administration than with the administration over a 30-to 60-minute period.

If AF appears in the context of LCM therapy, we recommend discontinuation of therapy and assessment to determine whether indefinite anticoagulant therapy should be started, according to a specific evaluation of embolic risk.

There are, however, a number of limitations to this paper. Since the sample size was only a single patient, conclusions and recommendations cannot be inferred. In addition, the presence of previous paroxysmal AF cannot be ruled out. Finally, it could be possible that AF and cerebral infarcts occurred hours before, leading to the clinical manifestations observed at the time of admission. However, this possibility does not seem probable in light of the provided arguments, the nature of the described clinical manifestations (similar to those described years ago), a normal left atrium based on a previous transthoracic echocardiogram, the initial EKG showing sinus rhythm, and the initial multimodal CT scan showing no data consistent with infarct or other remarkable signs.

Conclusions

LCM is an effective and well-tolerated AED, and it is becoming increasingly more popular even for off-label indications. In addition to its well-described adverse events, its usage at different dosages and via different routes of administration may provoke infrequent arrhythmic events such as AF and atrial flutter. Given the severe clinical and therapeutic implications that may follow, the use of LCM might be re-evaluated within a context of increased predisposition to developing AF, particularly if alternative AEDs are available. In the event of AF during therapy with LCM, this should be discontinued and the need for indefinite anticoagulant therapy should be assessed depending on the embolic risk for the patient. Further investigation is needed in order to establish stronger recommendations regarding the use of LCM within the context of a high risk of AF. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.
We express our gratitude to the patient and his family for their collaboration and also to the other healthcare workers involved in the care of the patient.
None of the authors have any conflicts of interest to declare.

References

Abou-Khalil BW. Antiepileptic drugs. *Continuum (Minneap Minn)* 2016; 22(1): 132-56.

Ay H, Benner T, Arsava EM, *et al*. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. *Stroke* 2007; 38: 2979-84.

Benjamin EJ, Levy D, Vaziri SM, *et al*. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994; 271(11): 840-4.

Ben-Menachem E, Biton V, Jatuzis D, *et al*. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007; 48: 1308-17.

Chung S, Sperling MR, Biton V, *et al*. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. *Epilepsia* 2010; 51: 958-67.

DeGiorgio CM. Atrial flutter/atrial fibrillation associated with lacosamide for partial seizures. *Epilepsy Behav* 2010; 18: 322-4.

Fountain NB, Krauss G, Isojarvi J, *et al*. Safety and tolerability of adjunctive lacosamide intravenous loading dose in lacosamide-naïve patients with partial-onset seizures. *Epilepsia* 2013; 54(1): 58-65.

Glotzer TV, Ziegler PD. Silent atrial fibrillation as a stroke risk factor and anticoagulation indication. *Can J Cardiol* 2013; 29(7): S14-23.

Gosh S, Jehi LE. New-onset epilepsy in the elderly: challenges for the internist. *Cleve Clin J Med* 2014; 81(8): 490-8.

Guldiken B, Rémi J, Noachtar S. Cardiovascular adverse effects of phenytoin. *J Neurol* 2016; 263: 861-70.

Halasz P, Kälviänen R, Mazurkiewicz-Beldzinska M, *et al*. Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. *Epilepsia* 2009; 50: 443-53.

Hansen CC, Ljung H, Brodtkorb E, Reimers A. Mechanisms underlying aggressive behaviour induced by antiepileptic drugs: focus on topiramate, levetiracetam and perampanel. *Behav Neurol* 2018; 2018: 2064027.

Kaufman KR, Velez AE, Wong S, *et al*. Low-dose lacosamide-induced atrial fibrillation: case analysis with literature review. *Epilepsy Behav Case Rep* 2013; 1: 22-5.

Kirchhof P, Benussi S, Kotecha D, *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016; 37(38): 2893-962.

Krause LU, Brodowski KO, Kellinghaus C. Atrioventricular block following lacosamide intoxication. *Epilepsy Behav* 2011; 20(4): 725-7.

Lehtonen AO, Langén VL, Porthan K, *et al*. Electrocardiographic predictors of atrial fibrillation in non-hypertensive and hypertensive individuals. *J Hypertens* 2018; 36(9): 1874-81.

Leitinger M, Beniczky S, Rohracher A, *et al*. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus-approach to clinical application. *Epilepsy Behav* 2015; 49: 158-63.

Mercadé Cerdá JM, Toledo Argani M, Mauri Llerda JA, *et al*. Guía oficial de la Sociedad Española de Neurología de práctica clínica en epilepsia. *Neurología* 2016; 31(2): 71-142.

Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem* 2013; 46(15): 323-38.

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.

Nguyen KT, Vittinghoff E, Dewland TA, *et al*. Electrocardiographic predictors of incident atrial fibrillation. *Am J Cardiol* 2016; 118(5): 714-9.

Nizam A, Mylavarapu K, Thomas D, *et al*. Lacosamide-induced second-degree atrioventricular block in a patient with partial epilepsy. *Epilepsia* 2011; 52(10): e153-5.

Rogawski MA, Tofighy A, White HS, *et al*. Current understanding of the mechanism of action of the antiepileptic drug lacosamide. *Epilepsy Res* 2015; 110: 189-205.

Schlaug G, Siewert B, Benfield A, *et al*. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. *Neurology* 1997; 49(1): 113-9.

Shaibani A, Fares S, Selam J, *et al*. Lacosamide in painful diabetic neuropathy: an 18-week double blind placebo controlled trial. *Clin J Pain* 2009; 10: 818-28.

Shmuely S, van der Lende M, Lamberts RJ, *et al*. The heart of epilepsy: current views and future concepts. *Seizure* 2017; 44: 176-83.

Strzelczyk A, Zöllner JP, Willems LM, *et al*. Lacosamide in status epilepticus: systematic review of current evidence. *Epilepsia* 2017; 58(6): 933-50.

Surges R, Moskau S, Viebahn B, *et al*. Prolonged atrial fibrillation following generalized tonic-clonic seizures. *Seizure* 2012; 21(8): 643-5.

UCB Pharma. *Vimpat Prescribing Information*. June 2019.

Uhm JS, Shim J, Wi J, *et al*. First-degree atrioventricular block is associated with advanced atrioventricular block, atrial fibrillation and left ventricular dysfunction in patients with hypertension. *J Hypertens* 2014; 32(5): 1115-20.

Van der Lende M, Surges R, Sander JW, *et al*. Cardiac arrhythmias during or after epileptic seizures. *J Neurol Neurosurg Psychiatry* 2016; 87(1): 69-74.

Wang X, Yu Y, Ma R, *et al*. Lacosamide modulates collapsin response mediator protein 2 and inhibits mossy fiber sprouting after kainic acid-induced status epilepticus. *Neuroreport* 2018; 29(16): 1384-90.

Wymer JP, Simpson J, Sen D, *et al*. Efficacy and safety of lacosamide in diabetic neuropathic pain: an 18-week double blind placebo-controlled trial of fixed-dose regimens. *Clin J Pain* 2009; 25: 376-85.

TEST YOURSELF

(1) Is AF an adverse reaction to be expected in the context of LCM administration?

(2) Is it recommended to assess the patient's risk of developing AF before the administration of LCM?

(3) What should one do if AF appears in the context of LCM therapy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".