■ Clinical vignette

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Epileptic Disorders

Lacosamide-induced symptomatic sinus node dysfunction

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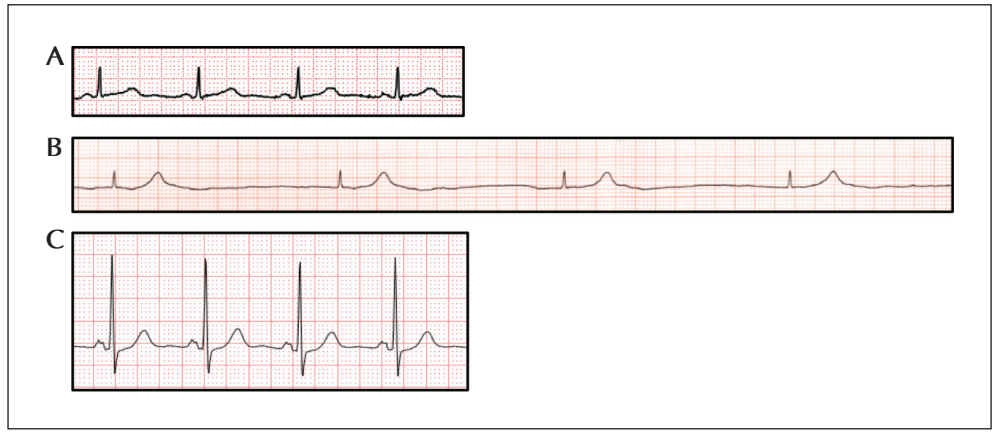
A 78-year-old, 60-kg man, with a history of chronic renal impairment, paroxysmal atrial fibrillation, bilateral subdural abscesses, and subsequent symptomatic epilepsy, was brought to our hospital due to syncope. He had been started on lacosamide, at 100 mg/day, in addition to levetiracetam, at 1,000 mg/day, for symptomatic epilepsy four weeks earlier, and electrocardiogram (ECG) at that point showed normal sinus rhythm, heart rate of 65 beats/min, and PR interval of 0.16 seconds (*figure 1A*). The lacosamide dose had been increased to 200 mg/day to achieve the maintenance dose one week earlier, but he began to feel dizzy the day after the lacosamide dose increase and eventually fainted. On arrival, ECG showed bradycardia with a heart rate of 26 beats/min, along with junctional escape rhythm (*figure 1B*), for which a temporary pacemaker was urgently inserted. Laboratory data showed decreased renal function, with an estimated glomerular filtration rate (eGFR) of 40 mL/min/1.73 m^2 (creatinine clearance: 38 mL/min), and no obvious abnormalities regarding either serum electrolyte or thyroid hormone levels. His regular medications on admission included lacosamide, 200 mg/day, levetiracetam, 1,000 mg/day, edoxaban, 30 mg/day, telmisartan, 80 mg/day, and amlodipine, 5 mg/day. Suspecting the possible drug effect of lacosamide, we discontinued lacosamide as well as the antihypertensive drugs. From Day 2, he began to have self-pulsations, and ECG showed normal sinus rhythm with a heart rate of 70 beats/min (*figure 1C*). A Holter ECG and ECG monitoring showed no more bradycardia or recurrence of pauses, and the temporary pacemaker was removed on Day 6. Thereafter, telmisartan and amlodipine were restarted and valproic acid was added for his residual epileptic symptoms; he was discharged home on Day 16. He has had no further fainting episodes or bradycardia on ECG follow-up in the two months since discharge.

Lacosamide is an AED that exerts anticonvulsant effects by slow inactivation of voltage-gated sodium channels. Lacosamide-associated arrhythmias in previous reports included atrial fibrillation/flutter [1], sinus node dysfunction [2], second- or third-degree atrioventricular block [3-5], ventricular tachycardia [6], and cardiac arrest [7, 8]. Although a case of sinus node dysfunction has been reported, it was asymptomatic and was observed under the high dose of 500 mg/day lacosamide (therapeutic range with normal renal function: 200-400 mg/day) [2]. In some of the reported cases of arrhythmias in patients receiving low lacosamide doses, the possibility of interaction with other sodium channel blockers or drugs that have negative effects on cardiac conduction (such as bisoprolol and cyclobenzaprine) was suggested [4, 7]. In addition to high drug doses, impaired renal function, a history of cardiac disease, and advanced age have been listed as risk factors for arrhythmias with lacosamide [4-6].

This is the first reported case of a patient with symptomatic sinus node dysfunction with therapeutic doses of lacosamide. Our patient developed presyncope symptoms the day after the



■ **Figure 1.** ECG readings showing normal sinus rhythm, heart rate of 65 beats/min, and PR interval of 0.16 seconds, three weeks prior to admission (A); bradycardia with a heart rate of 26 beats/min, along with junctional escape rhythm on arrival to the hospital (B); and normal sinus rhythm with a heart rate of 70 beats/min, following discontinuation of lacosamide and antihypertensive drugs (C).

lacosamide dose was increased to 200 mg/day, and sinus node dysfunction improved the day after discontinuation of lacosamide, strongly suggesting that it was the inducing factor. According to the prescribing information approved by the US Food and Drug Administration, the elimination half-time of lacosamide is approximately 13 hours, which supports the relationship between our patient's clinical course and the known pharmacokinetics of the drug. Although drug interactions cannot be ruled out as the cause of our patient's symptoms, because the patient was concomitantly receiving other medications, unlike previous reports, he was not on drugs with obvious cardiac depressant effects or other sodium channel blockers.

Although there are few reports of similar arrhythmias with lacosamide, and lacosamide is well tolerated by the majority of patients, the possibility of serious cardiac adverse effects occurring in some individuals needs to be considered, even at dosages within the approved dose range. Since sinus node dysfunction and atrial fibrillation are both expressions of atrial dysfunction and their co-existence is not uncommon, the history of paroxysmal atrial fibrillation in our patient could have been a risk factor for the development of bradycardia after increasing the dose of lacosamide. In many cardiac tissues, the action potential rises via sodium channels, especially in the non-nodal region, and it is possible that the conduction velocity delay becomes more pronounced with increasing lacosamide concentrations [2, 3]. If the conduction velocity decreases drastically, an impulse generated by the sinus node might not be transmitted through the surrounding atrial tissue at all, as in this case, causing a slow junctional escape rhythm. Our patient was an elderly man with chronic mild-to-moderate renal dysfunction, which implies decreased lacosamide clearance and a correspondingly higher serum lacosamide concentration compared with individuals with normal renal function. This could have triggered the development of sinus node dysfunction even with a relatively low dose of lacosamide. Our report reinforces the importance of exerting particular caution when using lacosamide in those with risk factors for cardiac adverse effects, such as old age, impaired renal function, pre-existing cardiac disease, or concomitant intake of other sodium channel blockers or certain other drugs affecting cardiac electrophysiology. In patients taking other sodium channel-blocking antiseizure drugs, in particular, physicians may consider reducing their dosage when lacosamide is started, or, alternatively, using another antiseizure medication instead of lacosamide.

In conclusion, the efficacy and safety of lacosamide have been shown in previous studies, and it should be emphasized again that serious cardiac disturbance is an exceptional adverse effect. However, lacosamide might cause unexpected adverse effects in patients with age-related renal dysfunction. In elderly patients receiving lacosamide, the dose should be reviewed with regular ECG and renal function monitoring, even if it is within the therapeutic range. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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Availability of data and material.
The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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TEST YOURSELF

(1) What is the mechanism of the antiepileptic action of lacosamide?

(2) What are some of the rare but serious adverse effects of lacosamide?

(3) What should be performed routinely when administrating lacosamide in the elderly?

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