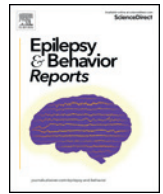




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Case Report

Lacosamide-associated second-degree atrioventricular block in a healthy, young athlete



Brian Stamm*, Atif Sheikh, Stephan Schuele, Jessica W. Templer

Northwestern University Feinberg School of Medicine, Department of Neurology, Chicago, IL 60611, United States

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ABSTRACT

Lacosamide enhances slow inactivation of voltage-gated sodium channels and can lead to dose-dependent PR interval prolongation. Previously, lacosamide has been associated with second-degree atrioventricular (AV) heart block in the context of multiple medical comorbidities and/or in the elderly with multimorbidity on other dromotropic agents. We report a case of second-degree AV block occurring in a healthy, athletic young adult. The patient had baseline bradycardia with no known cardiac comorbidities. He was exquisitely sensitive to lacosamide with EKG and telemetry changes developing on the order of hours after receiving intravenous lacosamide. Lacosamide was subsequently stopped, the second-degree AV block was no longer present and EKG returned to baseline. We hypothesize that his sensitivity to lacosamide-induced AV block was possibly secondary to his baseline bradycardia with early repolarization changes. The case underscores the importance of surveillance cardiac monitoring. While medical comorbidities and an older age may portend a greater risk of PR prolongation, routine EKGs should be considered in all patients receiving lacosamide.

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1. Introduction

Lacosamide was approved for use in 2008 by the U.S. Food and Drug Administration for adjunctive treatment of focal and secondarily generalized seizures [1]. In part, lacosamide works by enhancing slow inactivation of voltage-gated sodium channels [2]. While pooled studies have evaluated the cardiac safety of lacosamide and shown dose-dependent PR interval prolongation, second-degree atrioventricular (AV) heart block was not observed in these studies [3] and has only been described in a single case report, in a medically complex patient receiving other PR-prolonging agents [4]. Lacosamide-associated complete heart block has also been demonstrated in several cases of elderly patients with multimorbidity on other dromotropic agents [5–7]. In contrast, we report a case of second-degree AV block in a healthy, athletic young adult with drug-resistant epilepsy, baseline bradycardia, lupus profundus, and no other comorbidities. The patient was exquisitely sensitive to lacosamide with EKG and telemetry changes developing on the order of hours after receiving intravenous lacosamide. Once lacosamide was stopped, the patient's EKG returned to baseline.

2. Case report

The patient is a 32-year-old healthy right-handed male with a prior history of biopsy-confirmed lupus profundus (but no evidence of systemic lupus erythematosus) and drug-resistant left temporal lobe epilepsy with focal impaired awareness seizures, admitted to the epilepsy monitoring unit (EMU). Neuroimaging was unremarkable. The patient's cardiac history was notable for baseline sinus bradycardia and early repolarization (demonstrated on multiple EKGs in the preceding years). These EKGs had presumably been obtained in the setting of his prior rheumatologic evaluations and because he was previously taking hydroxychloroquine and methotrexate for lupus profundus. At the time of his EMU admission, he had not been taking immunosuppressants for several months. He had never had cardiac symptoms other than occasional, intermittent palpitations. He had no significant cardiac family history and no family history of sudden death.

The patient's antiseizure regimen upon admission to the EMU was lacosamide three times a day (TID; 100 mg, 200 mg, 100 mg), lamotrigine 100 mg TID, levetiracetam 1000 mg TID, and clonazepam 1 mg TID (TID dosing was preferred by the patient). Lacosamide level on admission was 3.8 mcg/mL (normal range: up to 15.0 mcg/mL; level approximately 3 weeks prior was 6.1 mcg/mL); lamotrigine on admission 2.6 mcg/mL (normal range: 4.0–18.0 mcg/mL; 3 weeks prior 6.0 mcg/mL); and levetiracetam on admission 7.6 mcg/mL (normal range: 12.0–46.0 mcg/mL). His admission labs were within normal limits, including a normal potassium (3.9 mEq/L; normal range: 3.5–5.1 mEq/L).

* Corresponding author at: Northwestern Memorial Hospital, 251 E Huron St, Chicago, IL 60611, United States.

E-mail addresses: brian.stamm@northwestern.edu (B. Stamm), atif.sheikh@northwestern.edu (A. Sheikh), sschuele@nm.org (S. Schuele), Jessica.Templer@nm.org (J.W. Templer).

EKG on admission revealed prolonged PR interval (214 ms; normal PR interval is 120–200 ms) with first-degree AV block, as well as early repolarization with J-point elevations in several leads (Fig. 1A). QRS duration and QT interval were within normal limits. The case was discussed with the cardiology consult team who recommended standard cardiac monitoring but no other acute interventions, and patient was placed on continuous telemetry. On day one, lacosamide and levetiracetam were held as part of his diagnostic EMU evaluation. On day two, lamotrigine was held and clonazepam was reduced to 0.5 mg TID. Day two EKG showed normalized PR interval to 170 ms with sinus bradycardia (Fig. 1B). On day three, after diagnostic evaluation was completed, medications were resumed and lacosamide 150 mg IV, lamotrigine 200 mg PO, and levetiracetam 2 g IV were administered. That evening, he received lacosamide 150 mg, lamotrigine 100 mg, levetiracetam 1000 mg, and clonazepam 0.5 mg. Over the course of the evening, telemetry revealed frequent second degree, Mobitz type 1 AV

block (Wenckebach), defined by progressively lengthening PR interval and ultimately, the P wave is not conducted, in contrast to Mobitz type 2 AV block in which dropped beats occur sporadically without antecedent progressive PR prolongation (Fig. 2).

On day four, repeat EKG again showed prolongation of PR interval to 204 ms. Given these findings, lacosamide was discontinued on day four. Telemetry overnight from day four to day five showed no evidence of second-degree AV block, and EKG obtained on day five showed nearly normal PR interval (200 ms). Unfortunately, the patient never received follow-up EKGs despite our recommendations.

3. Discussion

Dose-dependent PR prolongation is a known side effect of lacosamide and has been demonstrated in pooled data from randomized-controlled trials [3], but AV heart block secondary to the

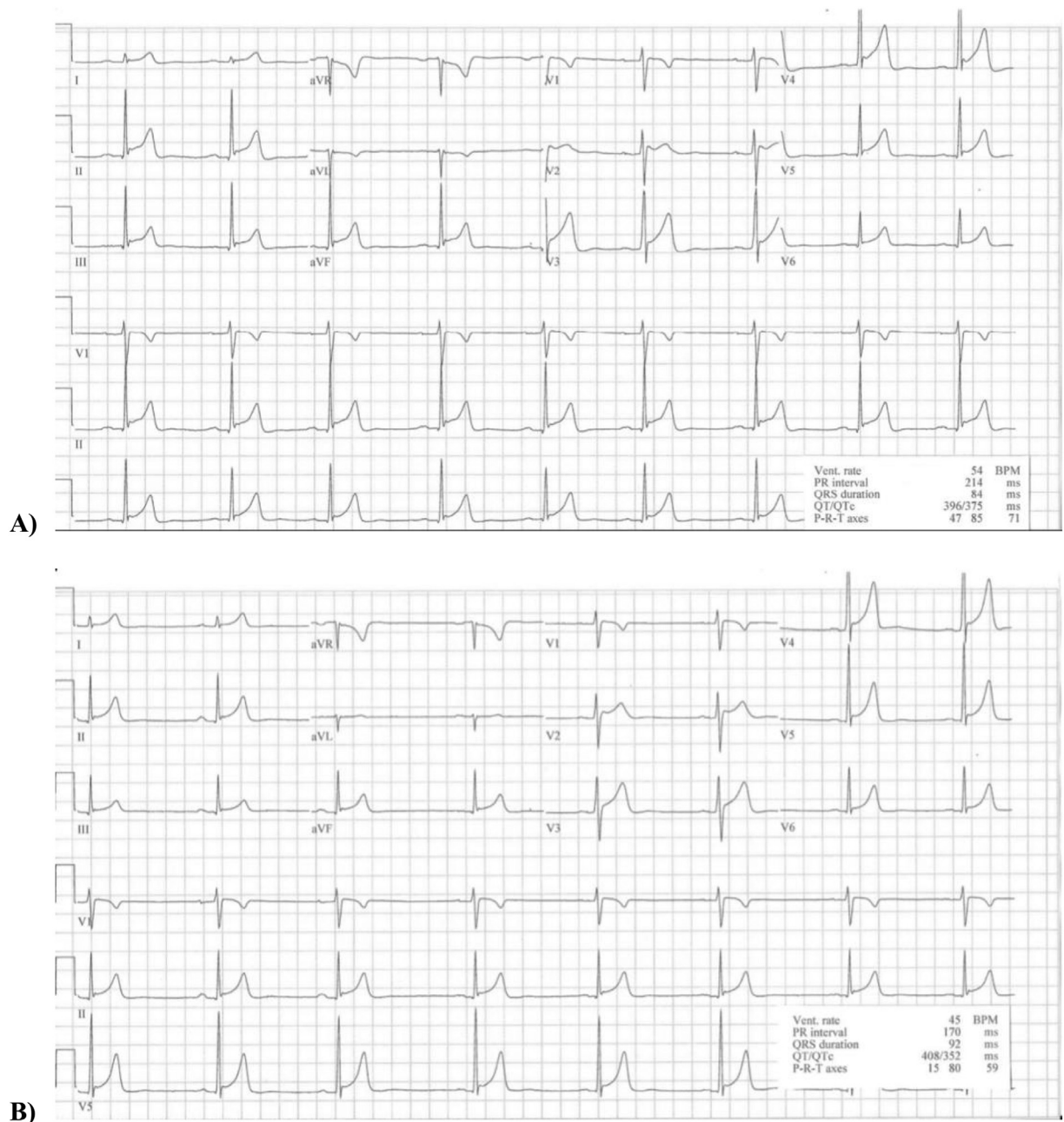


Fig. 1. Representative EKGs. A) Day one EKG with first-degree atrioventricular (AV) block, as well as early repolarization with J-point elevations in several leads. B) Day two EKG with normalized PR interval to 170 ms with sinus bradycardia.

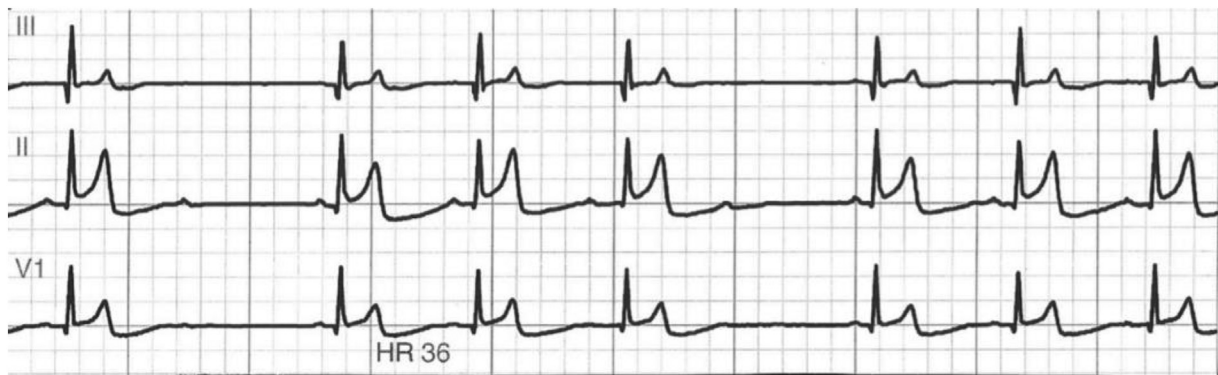


Fig. 2. Day four representative telemetry tracing showing second degree, Mobitz type 1 AV block (Wenckebach).

medication is a rare phenomenon demonstrated previously only in case reports. The previously published cases, as summarized in Table 1, are largely confined to older, multimorbid patients taking additional dromotropic medications known to prolong the PR interval [4–8].

When compared with these previously published cases, our patient is unique in that he is the youngest, overall healthiest, and was exquisitely sensitive to the medication with respect to time scale of AV nodal changes. While the other cases were complicated by multiple comorbidities, our patient's only notable medical history was lupus profundus, an uncommon form of chronic cutaneous lupus erythematosus (CCLE). While systemic lupus erythematosus (SLE) has a widely recognized association with heart block, and SLE co-occurs in approximately 10% of lupus profundus cases [9,10], our patient had been evaluated by rheumatology and did not meet diagnostic criteria for SLE and notably had a negative antinuclear antibody test during his EMU admission.

All of the previously reported patients were taking other dromotropic medications in addition to lacosamide. Though our patient was additionally taking lamotrigine—which also acts on sodium channels—this medication has been shown to only slightly prolong the PR interval, namely at high doses. Also, the above-described changes largely occurred while lamotrigine was being held constant.

The temporal correlation of lacosamide with prolonged PR interval and AV block was particularly striking in this case with AV block resolving within 12 h of lacosamide cessation and PR normalization occurring within 36 h. This time scale is impressive given lacosamide's approximate elimination half-life of 13 h. Whereas many of the prior cases had comorbid renal dysfunction, our patient's preserved renal function

may have led to more rapid clearance of the medication and thus quicker resolution of the pathologic EKG findings.

Interestingly, our patient fits the phenotype of a healthy, young athlete with an admission EKG showing J-point elevations consistent with early repolarization changes. Studies have shown that prevalence of J-point elevation in athletes tends to be higher than that of the general population [11], thought to be related to a physiological balance favoring parasympathetic tone [12]. One cross-sectional study found that former National Football League players had, on average, lower resting heart rates and a higher prevalence of first-degree atrioventricular block than healthy controls [13]. Finally, reports of sudden cardiac death in athletes have gained attention in recent years, with some cases attributed to conduction abnormalities, but the more predominant etiology being hypertrophic cardiomyopathy [14]. In summary, in addition to his preserved renal function, our patient's repolarization abnormalities, baseline bradycardia, and overall tendency towards increased parasympathetic tone may have predisposed him to his exquisite sensitivity towards lacosamide.

This case demonstrates a unique departure from prior reports of lacosamide-associated heart block because this patient was relatively young and had minimal baseline medical complexity compared with prior cases. Awareness of lacosamide-associated heart block is particularly important now given its increasing use in status epilepticus due to the drug's intravenous availability [15]. Especially in status epilepticus, efficient administration of lacosamide is paramount, and recent data suggests IV push has a similar adverse effect rate to IV piggyback preparation, with the same rates of PR prolongation in each group [16]. Regardless of route of administration, this case should serve as a

Table 1

Literature summary of cases of lacosamide-associated atrioventricular block, with the current case listed first.

Age & gender	Past or concurrent medical history	Seizure localization	LCM dosing, formulation	Notable other meds	PR; heart block type	Time to PR normalization/resolution of EKG abnormalities	Outcome
32 M	Lupus profundus	Left temporal lobe	400 mg/day PO	LTG	2nd degree	~12 h for AV block resolution; 36 h for PR normalization	Complete recovery
45 M	Craniopharyngioma s/p craniotomy c/b panhypopituitarism; ALL	Right frontal lobe	200 mg/day PO	CBZ, levothyroxine	2nd degree	19 h for AV block resolution; 3 days for PR normalization	PPM placement; complete recovery [4]
49 F	Hypothyroidism	Focal, unspecified	500 mg/day PO	CBZ, levothyroxine	Sinus pauses; junctional escape rhythm	4 days for sinus pause normalization	Complete recovery [8]
71 F	HTN, development of renal & hepatic failure	Focal, unspecified	300 mg/day PO	Metoprolol	3rd degree	2 days for resolution of complete heart block	Temporary PPM placement [6]
88 F	HTN	Unspecified	100 mg/day PO	Bisoprolol	3rd degree	Unknown	PPM placement [7]
89 F	HF, HTN, kidney dysfunction, hypothyroidism	Nonconvulsive status	800 mg IV	Metoprolol, amlodipine, levothyroxine	3rd degree	Within 24 h for PR normalization	Death 2/2 respiratory failure [5]

Abbreviations: LCM, lacosamide; M, male; PO, *per os*; LTG, lamotrigine; AV, atrioventricular; s/p, status post; c/b, complicated by; ALL, acute lymphocytic leukemia; CBZ, carbamazepine; PPM, pacemaker; F, female; HTN, hypertension; HF, heart failure; IV, intravenous; 2/2, secondary to.

reminder of the importance of cardiac monitoring with new or altered dosing of lacosamide, even—or perhaps particularly—in healthy, young athletes.

4. Conclusion

We report a case of lacosamide-associated, second-degree AV block in a healthy, athletic young adult. This case differs from the preexisting literature, as our patient had no major medical comorbidities and was exquisitely sensitive to lacosamide with EKG and telemetry changes developing within hours of administration and rapid resolution with stopping lacosamide. Monitoring of cardiac function is important in all patients taking lacosamide, irrespective of age and medical comorbidities.

Contributions

Brian Stamm: Conceptualization, Investigation, Writing – original draft preparation. **Atif Sheikh:** Writing – review and editing. **Stephan Schuele:** Supervision, Writing – review and editing. **Jessica Templer:** Supervision, Writing – review and editing.

Ethical statement

No experimentation was conducted on human subjects (our study is a case report) and thus informed consent was not obtained.

Declaration of competing interest

Dr. Schuele is on the speaker's bureau for Eisai Inc., Sunovion, and Greenwich.

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None.

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