High-grade Atrioventricular Block Due to Lacosamide and Tizanidine Combination Therapy for Epilepsy and Multiple Sclerosis

INTRODUCTION

High-grade atrioventricular (AV) heart block is characterized by complete dissociation of the electrical activity of the atrium and ventricle that can manifest in different settings with varying symptomatology and severity [1]. Although the escape rhythm can mostly compensate it from the distal part of the block, severe and life-threatening consequences like syncope and death may occur. Among several causes, drug-induced AV block can be observed either in the recommended dose, overdose, or a combination of responsible drugs that may require temporary or permanent pacing. Drug-induced AV block can be transient, persistent, or recurrent [2]. However, there was scarce data about the monitorization, management, and follow-up strategy of drug-induced AV block patients after an index event. Herein, we presented our approach to a patient admitted to our emergency room with a high-grade AV block due to lacosamide and tizanidine medications.

CASE

A 51-year-old female patient was admitted to our emergency room with a sudden-onset epileptic seizure. Past medical history revealed the diagnosis of epilepsy and multiple sclerosis for four years. She has been regularly taking medications of acetylsalicylic acid 1x300 mg, tizanidine 2x6 mg, lacosamide 2x200 mg, levetiracetam 2x1500 mg, and baclofen 1x10 mg. There was no suspicion of a drug overdose. Physical examination, including vital signs, was unremarkable except for a pulse rate of 40 bpm. 12-lead electrocardiography (ECG) on admission showed a complete AV block (ventricular rate of 33 bpm) (Figure 1A). Laboratory test results, including electrolytes, were within normal reference limits. A bedside emergent echocardiography indicated normal findings. Defibrillator patches with a cutaneous temporary pacing ability (back-up rate of 40 bpm) were applied and closely followed in the emergency room. However, spontaneous sinus rhythm was observed after one hour of admission (ventricular rate of 76 bpm) (Figure 1B). The Naranjo Algorithm,
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or Adverse Drug Reaction Probability Scale [3] total score was calculated as 7 for our patients which proposed that there was a probable adverse drug reaction for those suspected drugs of “lacosamide and tizanidine”. Because of previously published case reports, tizanidine was stopped immediately. Lacosamide was also replaced with valproic acid after an electroencephalography (EEG) test after a neurology consultation. She closely monitored and followed for the recurrence of seizures. However, the patient developed Mobitz type 2 second-degree AV block with a ventricular rate of 45 bpm at the 22nd hour of follow-up (Figure 2A). The patient returned to spontaneous sinus rhythm (ventricular rate of 97 bpm) after 10 minutes of a close monitorization (Figure 2B). After a 48-hours duration of hospitalization and monitoring for heart rhythm, she was discharged uneventfully. A 48-hour Holter monitorization at the 7th-day control visit showed no bradyarrhythmia.

Figure 1. A) 12-lead electrocardiography of the patient on admission to the emergency room was consistent with complete AV block. B) Spontaneous sinus rhythm was observed after one-hour of admission.
DISCUSSION

Transient or persistent advanced second-degree and third-degree AV block may occur in various clinical situations like acute myocardial infarction, and electrolyte imbalance such as hyperkalemia and after radiofrequency catheter ablation. It may be life-threatening if the underlying cause is not resolved. Drugs, including beta-blockers, calcium channel blocking agents, digoxin, and antiarrhythmic drugs, are the leading causes. Still, on the other hand, AV block may occur related to medications that are not used for their cardiac effects like antiepileptic drugs. Elderly patients are more often on polypharmacy and have more extensive comorbidity, and this population has more structural heart disease and conduction abnormalities. These conditions increase the risk of adverse drug effects through drug-drug or drug-disease interactions and abnormal pharmacokinetics [4]. A significant percentage of all these reactions involve the cardiovascular system, the most frequent drug-related cardiovascular abnormality, is probably bradycardia [5].

Figure 2. A) The patient developed Mobitz type 2 second-degree AV block with a ventricular rate of 45 bpm at the 22nd hour of follow-up. B) The patient returned to spontaneous sinus rhythm after 10 minutes of a close monitorization.
Drug-induced AV block is potentially reversible but inadequately characterized by bradyarrhythmia reason [6]. It is not known if patients can expect a benign course after cessation of the responsible drug. In a common clinical approach, drug-induced advanced AV block can be reversible with drug discontinuation, and patients who are symptomatic or hemodynamically unstable require temporary pacing. The long-term prognosis remains unclear. Moreover, it is little known what proportion of patients have a recurrence and need permanent pacemaker implantation.

In our case, the patient had a history of using lacosamide and tizanidine. Lacosamide (LCM) is developed for use as an antiepileptic drug. It is currently indicated as an adjunctive treatment for partial-onset seizures in adults with focal epilepsy, especially in patients who are unresponsive to conventional therapies. Off-label use is seen in status epilepticus. LCM is eliminated primarily by the kidneys (elimination half-life 15-23 hours) and can be used orally and intravenously with a maximum daily dose of 400 mg, typically divided twice daily [7,8] LCM is associated with dose-dependent PR interval prolongation which can result from AV nodal or infra-Hisian conduction delay due to its effect on voltage-gated sodium channels. However, action potential generation in the AV node is mediated through voltage-gated Ca2+ channels, with the sodium current playing a minimal role. Potential LCM effects on calcium currents or autonomic tone may result in direct AV nodal effects causing varying degrees of atrioventricular block [9]. Sinus bradycardia and ventricular tachycardia may also occur. Adverse cardiac effects are more severe with overdose than in the therapeutic dose range and mainly seen during the titration period [10]. Lachuer et al.[11] reported that an 88-year-old female patient with hypertension and angina developed 3rd-degree AV block after taking the only initial dose of lacosamide. Furthermore, Stamm et al.[12] reported a case of second-degree AV block occurring within hours after intravenous lacosamide and improvement after withdrawal of the drug in a healthy, athletic young adult who had baseline bradycardia with no known cardiac comorbidities. Tizanidine is also used as a muscle relaxant and acts centrally to agonize a-2 autoreceptors (elimination half-life 2-4 hours) [13]. It can cause dizziness, hypotension, and severe bradycardia. Cortes et al.[13] reported a case of a 93-year-old female patient that developed profound hypotension and bradycardia that require permanent pacing after a single dose of tizanidine. In our case, there was no suspicion of a drug overdose, and 3rd-degree AV block was seen in the therapeutic dose range. The patient was using lacosamide and tizanidine for three years in the same dosage. It was evident from previous reports that these drugs might cause bradyarrhythmia or AV block in the therapeutic range. However, the essential triggering factor for advanced AV block in our patient was unclear. We thought that epileptic seizure itself might modulate autonomic nerve activity [14,15] and AV conduction might be inhibited by epileptic origin in the brain like temporal lobe seizures [16]. Furthermore, using lacosamide and tizanidine medications probably facilitated the impact of epileptic seizure via autonomic modulation on AV conduction. However, recurrence of AV block at 22nd hour of follow-up without recurrence of epileptic seizure confirmed the dominant impact of lacosamide and tizanidine medications on AV block. Thus, we diagnosed the patient as drug-induced AV block.

Furthermore, there is no standard approach to the management of patients with drug-induced AV block. This situation seems to be benign and thought to be reversible with drug cessation. However, recurrences can be seen during follow-up, and some patients need permanent pacemaker implantation [17]. If possible, offending medications should be discontinued. At this point, the patient’s indication for drug use and whether there are alternative medicines are essential. Additional factors, such as underlying AV conduction abnormalities, may facilitate drug-induced AV block development. So considering all these factors, an individual decision must be made for each patient. Therefore, the LCM was replaced with valproic acid, and tizanidine was discontinued in our patient in whom no recurrence of AV block was observed at early follow-up.

Author contribution
Study conception and design: SK and UC; data collection: SK and UC; analysis and interpretation of results: SK and UC; draft manuscript preparation: SK and UC. All authors reviewed the results and approved the final version of the manuscript.
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N/A as the paper was a case report

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REFERENCES


