Life Threatening Iatrogenic Bradycardia Related To The Use of Beta-Blockers Or in Combination With Other Antiarrhythmic Agents In Elderly Patients

Nabil Naser

Polyclinic „Dr. Nabil", Sarajevo, Sarajevo, Bosnia and Herzegovina.

Corresponding author: Assoc. Prof. Nabil Naser, MD, PhD, FACC, FESC, FEACVI. Polyclinic "Dr. Nabil", Sarajevo, Bosnia and Herzegovina. Tel: +387 33 777 711, fax: +38733 777 710. E-mail: nabil@ bih.net.ba. ORCID ID: http://www.orcid. org/0000-0002-278-8574.

Background: Drug-induced bradycardia is common during antiarrhythmic therapy; the major culprits are beta-blockers. However, whether other antiarrhythmic drugs are also a significant cause of this, alone or in combination with beta-blockers, is not well known. **Objective:** This study examined drugs that cause marked bradycardia in elderly patients in ambulatory settings. **Methods:** We retrospectively investigated the records of all patients at our Polyclinic for drug-related bradycardia from the years 2017 to 2023. Patients with arterial hypertension, chronic compensated heart failure, coronary artery disease, ischemic cardiomyopathies and other cardiac disease in whom the beta blockers were prescribed with other medications for treatment. **Results:** Nine patients were identified (mean age, 72±6 years; range, 65-81 years; 5 men). Four patients were taking only beta-blockers, while Five patients were on both beta-blockers and other antiarrhythmic drugs. Heart rates ranged from 23±47 beats/minute. The initial electrocardiogram showed sinus bradycardia (n= 5) or sinus arrest with escape beats (n=4). QRS duration was 80-105ms. The clinical presentation of the patients who taking beta-blockers and other antiarrhythmic drugs was considerably worse than that of the patients with only beta-blockers drugs and included worsening heart failure or presyncope or syncope. Four of the beta/blockers and other antiarrhythmic drugs group patients had been on their medications for over 12 months. In the Beta-blockers group only 3 patients recovered solely with drug discontinuation, while 3 patients in the BB + antiarrhythmic group needed additional treatments, such as intravenous administration of atropine or adrenergic agonist and temporary pacing. Three of all patients were referred to permanent implantation of pacemaker due to persistent life threatening bradycardia. **Conclusion:** Life-threatening bradycardia may occur in in the elderly with beta-blockers or combination therapy with other antiarrhythmic drugs in the elderly patients, even months after the start of medication, the recovery is challenging and, in some patients, permanent implantation of pacemakers is indicated due to persistent of severe bradycardia and symptoms of presyncope or syncope after discontinuation of medications.

Keywords: Iatrogenic bradycardia, life threating, elderly patients, QRS duration.

Dilemma, Received: Mar 02nd, 2023; Accepted: Mar 31st, 2023, doi: 10.5455/ijbh.2023.11.65-67, Int J Biomed Healthc. 2023; 11(1): 65-67

1. BACKGROUND

Drug-induced bradycardia is a serious and common but poorly characterized clinical problem. Clinically, severe bradycardia can be induced during therapy with beta-adrenergic blockers (beta-blockers), non-dihydropyridine calcium channel antagonists, and with any of the other classes of antiarrhythmic drugs.

Beta-blockers are the most common culprits of bradycardia, interfering with slow action potential generation and atrioventricular conduction. They target the sympathetic nervous system and have negative chronotropic and inotropic effects. In chronic heart failure, beta-blocker therapy protects the heart against cardiotoxic overstimulation by catecholamines, improving left ventricular function and performance. Such therapy also improves survival and reduces arrhythmia risk (sudden cardiac death). Their negative chronotropic effects could slow down the heart rhythm to an unexpected degree

2. OBJECTIVE

This study examined drugs that cause marked bradycardia in elderly patients in ambulatory settings.

3. MATERIAL AND METHODS

In this retrospective study, we reviewed all patients that visited our polyclinic between June 2017 and March 2023. These patients had a diagnosis of severe bradycardia associated with drug side effects. Patients were excluded if their bradycardia was attributed to cardiac disease, e.g., acute myocardial infarction, vasovagal syncope, cardiac myopathy, myocarditis, or failure of a previously implanted pacemaker device. We also excluded patients with electrolyte imbalances or hormonal abnormalities. The cause-and-effect relationship between medication use and bradycardia was determined from drug withdrawal response.

Patients group	Symptom	HR	HF	Urgent Treatment	Recover time hours	Serum K, mmol/L
BB group	Fatigue, dizziness, presyncope, syncope, dyspnea or chest discomfort	23–47	1 pts	Transcutaneous pacing, intravenous cardioactive medication	26	4.3
BB + other antiarrhythmic group	Inability to stand, syncope, severe dyspnea, Chest discomfort	21–46	2 pts	intravenous atropine Transcutaneous pacing	11	4.7

Table 1. Clinical presentation of all patients with iatrogenic bradycardia

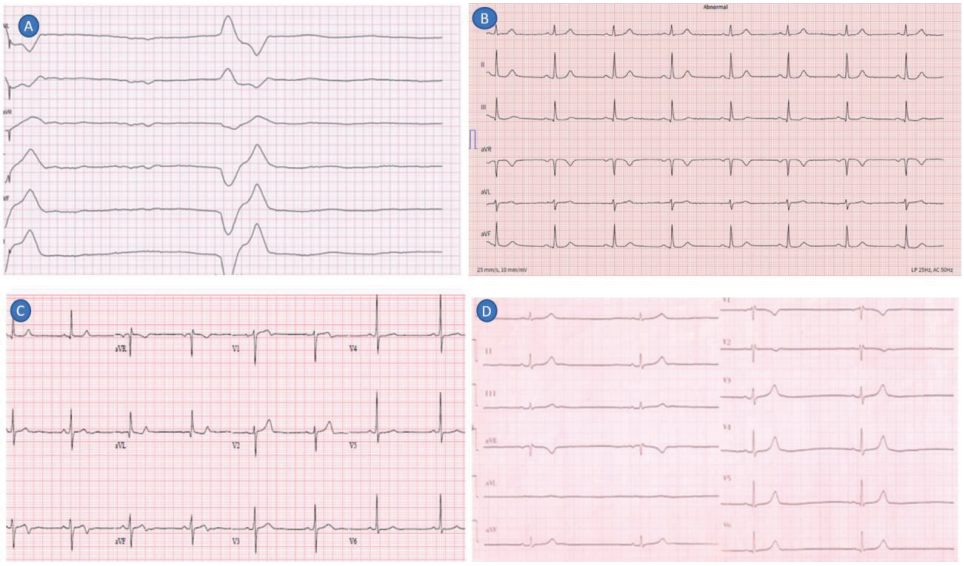

Figure 1. ECG records of patients with iatrogenic bradycardia. A. Severe bradycardia with heart rate of 23 bpm with extreme widening of the QRS complex. B. Sinus bradycardia with HR 47/min. C. Severe bradycardia with HR 38/min. D. Severe bradycardia with HR 22/min.

4. RESULTS

Nine patients were found who fulfilled our criteria for inclusion. Baseline characteristics of the study population as following: The mean age was 72±6 years (range, 65-81 years) and five patients were men. Five patients with regard to antiarrhythmic medications, four patients were taking beta-blockers only, while four patients were on both beta-blockers and other antiarrhythmic agents. The beta-blockers were metoprolol (n=2), sotalol (n=2) and bisoprolol (n=1). The other antiarrhythmic drugs were Na channel blockers (n=2) and Ca channel blockers (n=2). The duration that the patients had been on these medications before their bradycardic event ranged from 3 months to 4 years

The most common presenting symptom was syncope. The patients' heart rates ranged from 24±47 beats/minute. The initial electrocardiogram (ECG) showed sinus bradycardia in six patients and sinus arrest with escape beats in 3 patients. The mean QRS duration was 92.6 ±9 ms (range, 80–105ms). Two- dimensional echocardiography was performed in all patients and showed a mean left ventricular ejection fraction of 62±13% (range,49-75%). The clinical presentation of the beta-blockers + other antiarrhythmic agents was considerably worse than that of the beta-blockers (BB) group and included three patients with cardiogenic shock and heart failure. All patients in the BB group were presented with presyncope or syncope and only 3 patients recovered solely with drug discontinuation. In contrast, in the BB + other antiarrhythmic agents, only two patients recovered solely with drug discontinuation, and the remaining two patients needed supportive medical treatment that included intravenous administration of atropine or adrenergic agonist; two patients required temporary pacing as well. The duration for full recovery after medication withdrawal was longer in the BB+ other antiarrhythmic agents (26.5±7 hours in the BB+ antiarrhythmics group vs 15.6± 7.1 hours in the BB group). Three of all patients were referred to permanent implantation of pacemaker due to persistent life threatening bradycardia.

5. DISCUSSION

Iatrogenic bradycardia is a potential problem that may contribute to increased mortality during antiarrhythmic therapy. Bradycardia is a possible side effect of all classes of antiarrhythmic drugs. (1 ,2) However, it is known that drug-induced bradycardia usually does not appear in patients with normal sinus node function and normal atrioventricular conduction. (6, 7) Previous reports found that advanced age, combined drug therapy, the period during the initial 24 hours after initiation of drug therapy, decreased systolic performance, and female were predictors of proarrhythmia (1, 2) while preexisting conduction disturbance, ventricular arrhythmia, and combined drug therapy were associated with drug-induced brady-

cardia in particular (4, 6).

Beta-blockers cause bradycardia by antagonizing catecholamines produced by sympathetic nerves at the cell receptor. Five of our patients were on beta-blockers metoprolol or carvedilol. Emergent bradycardia associated with metoprolol and carvedilol in clinical practice was 18 per 1000 person-years in one study. (8) In patients with heart failure, the incidence of life-threatening bradycardia induced by carvedilol was 0.9% (Carvedilol Prospective Randomized Cumulative Survival [COPERNICUS] study) (9) while the incidence of bradycardia necessitating withdrawal of metoprolol was very similar at 0.8% in the Metoprolol con- trolled release/extended release Randomized Intervention Trial (MERIT-HF). (10) None of our patients had heart failure or structural heart disease. It is known that Na channel blockers may suppress sinus node function. However, the ionic mechanisms responsible for this suppression have not been determined. (5, 16)

6. CONCLUSION

All of our patients were elderly and were taking beta-blockers at the time of presentation. Their ECGs exhibited 23-47/min heart rates. Life-threatening bradycardia may occur in in the elderly with beta-blockers or combination therapy with other antiarrhythmic drugs in the elderly patients, even months after the start of medication, the recovery is challenging and, in some patients, permanent implantation of pacemakers is indicated due to persistent of severe bradycardia and symptoms of presyncope or syncope after discontinuation of medications. Caution should be exercised in prescribing, especially in elderly patients.

- **Author+s contribution***: The author was involved in all steps of the preparation this article, including final proof-reading.*
- **Conflict of interest***: None declared.*
- **Financial support and sponsorship***: Nil.*

REFERENCES

1. Friedman PL, Stevenson WG. Proarrhythmia. Am J Cardiol. 1998; 82(8A):50N–58N.
2. Zipes DP. Proarrhythmic effect of antiarrhythmic drugs. Am J Cardiol. 1987; 59 (11) : E26–E31.
3. Maisel WH, Kuntz KM, Reimond SC, et al. Risk of initiating antiarrhythmic drug therapy for atrial fibrillation in patients admitted to a university hospital. Ann Intern Med. 1997; 127(4): 281–284.
4. Hauser TH, Pinto DS, Josephson ME, Zimetbaum P. Safety and feasibil ity of a clinical pathway for the outpatient initiation of antiarrhythmic medications in patients with atrial fibrillation or atrial flutter. Am J Cardiol. 2003; 91(12): 1437–1441.
5. Toeda T, Susa R, Saigawa T, et al. A case of sinus pause due to the proarrhythmia of pilsicainide. Jpn Heart J. 2000; 41(3): 405–410.
6. Essebag V, Hadjis T, Platt RW, Pilote L. Amiodarone and the risk of bradyarrhythmia requiring permanent pacemaker in elderly patients with atrial fibrillation and prior myocardial infarction. J Am Coll Cardiol. 2003; 41(2): 249–254.
7. Bigger JT Jr, Reiffel JA. Sick sinus syndrome. Annu Rev Med. 1979; 30(1): 91–118.
8. Shin J, Pharm D, Pletcher M. Risk of emergent bradycardia associated with the use of carvedilol and metoprolol in routine clinical practice. Am J Med. 2013; 126(9): 805–810.
9. Krum H1, Roecker EB, Mohacsi P, et al; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. JAMA. 2003; 289(6): 712–718.
10. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled- release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure. JAMA. 2000; 283(10): 1295-1302.
11. Maier SK, Westenbroek RE, Yamanushi TT, et al. An unexpected requirement for brain-type sodium channels for control of heart rate in the mouse sinoatrial node. Proc Natl Acad Sci U S A. 2003; 100(6): 3507–3512.
12. Lei M, Jones SA, Liu J, et al. Requirement of neuronal- and cardiac- type sodium channels for murine sinoatrial node pacemaking. J Physiol. 2004; 559(Pt 3): 835–848.
13. Bogdanov KY, Vinogradova TM, Lakatta EG. Sinoatrial nodal cell ryanodine receptor and Na+-Ca+2exchanger:molecular partners in pacemaker regulation. Circ Res. 2001; 88(12): 1254-1258.
14. Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med. 2009 ;15(4) :380–383.
15. Hwang HS, Hasdemir C, Laver D, et al. Inhibition of cardiac Ca2 release channels (RyR2) determines efficacy of class I antiarrhythmic drugs in catecholaminergic polymorphic ventricular tachycardia. Circ Arrhythm Electrophysiol. 2011; 4(2): 128-135.
16. Ishikawa T, Sumita S, Kimura K, et al. Sinus node recovery time assessment by the overdrive suppression test employing an intravenous injection of disopyramide phosphate. Europace. 2000; 2(1): 54–59.
17. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope. J Am Coll Cardiol. 2017; 70(5): e39-e110. doi: 10.1016 /j.jacc.2017.03.003
18. Masic I, Naser N, Zildzic M. Publich Health Aspects of COVID-19 Infection with Focus on Cardiovascular Diseases. Mater Sociomed. 2020; 32(1): 71-76. doi: 10.5455 / msm.2020.32 .71-76.
19. Naser N, Kulic M, Dilic M, Dzubur A, Durak A, Pepic E, Smajic E, Kusljugic Z. The Cumulative Incidence of Stroke, Myocardial infarction, Heart Failure and Sudden Cardiac Death in Patients with Atrial Fibrillation. Med Arch. 2017; 71(5): 316-319. doi:10.5455 /medarh.2017.71.316-319.
20. Masic I, Rahimic M, Dilic M, Kadribasic R, Toromanovic S. Socio-medical Characteristics of Coronary Disease in Bosnia and Herzegovina and the World. Mater Sociomed. 2011; 23(3): 171-183. doi: 10.5455/msm.2011.23.171-183.