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

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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 threatening, elderly patients, QRS duration.

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.
xtreme widening of the QRS complex, a 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.

Table 1. Clinical presentation of all patients with iatrogenic bradycardia

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

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±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.

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REFERENCES