Case Report

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Complete Heart Block Secondary to Concomitant Use of Metoprolol and Fluoxetine in a Case of Chronic Depression and Systemic Hypertension: A Case Report

Internal Medicine Section

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ABSTRACT

Bradyarrhythmia can be brought on by intrinsic or extrinsic causes that disrupt the cardiac conduction system, with iatrogenic drug usage being the most common extrinsic cause. Atrioventricular (AV) block is frequently brought on by beta-blockers, calcium channel blockers, anti-arrhythmics, and digoxin. The first course of treatment for heart block involves stopping the problematic medications. Psychotropic medications have the potential to cause cardiotoxic adverse effects that affect the heart. In a patient with a pre-existing cardiac disorder, psychotropic drugs can manifest with dangerous arrhythmias. It is yet unknown what intricate processes cause these effects. A variety of arrhythmias may be brought on by or made worse by many commonly used drugs. Hereby, the authors present a case report of 56-year-old hypertensive male, a known case of chronic depression with chest heaviness. The Electrocardiogram (ECG) revealed Complete Heart Block (CHB) with Right Bundle Branch Block (RBBB). The patient was on fluoxetine and beta-blockers for his mental illness and hypertension. Three days after withholding the drugs, the CHB resolved, and his baseline ECG remained as RBBB. The present case highlights the interaction of drugs leading to CHB in present patient. Therefore, the importance of a detailed drug history in such cases becomes imperative.

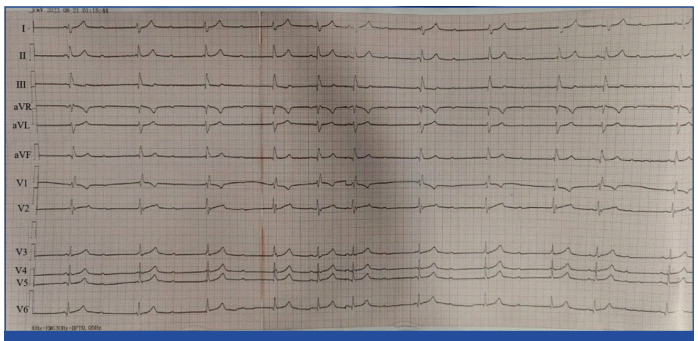
Keywords: Arrhythmias, Depressive disorder, Psychotropic drugs

CASE REPORT

A 56-year-old male patient presented to the hospital with complaints of chest heaviness for four hours. He was a known case of chronic depression for two months, for which he was taking tablet Fluoxetine 40 mg once daily, and was a case of systemic hypertension for one year, for which he was on tablet metoprolol 25 mg twice a day.

On examination in the Emergency Department of the hospital, the patient was conscious and oriented. His pulse was 36 beats per minute, which was regular, with normal volume, and blood pressure was 102 mmHg systolic and 58 mmHg diastolic. The rest of the general examination was normal. On examination of the cardiovascular system, heart sounds were normal. There were no S3, S4, or murmurs. Other system examinations were normal.

On investigations, the ECG was suggestive of RBBB with CHB [Table/Fig-1]. The patient was shifted to the cardiac Intensive Care Unit (ICU). All routine blood investigations, including cardiac biomarkers and serum electrolytes, were done, and they were within normal limits as shown in [Table/Fig-2]. A 2D echo ruled out any regional wall motion abnormality.



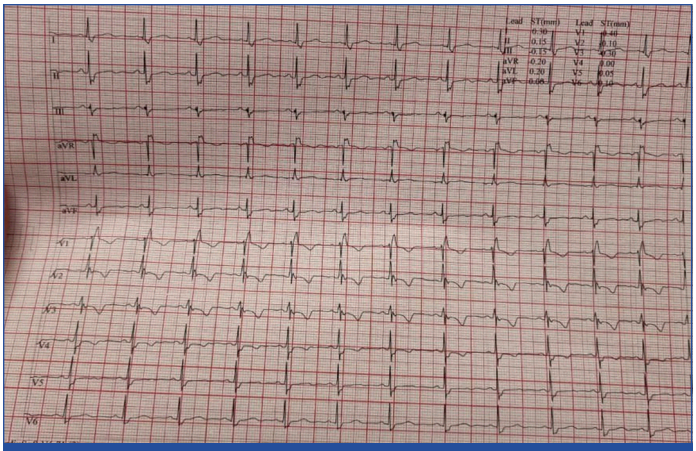
[Table/Fig-1]: ECG of the patient on presentation.

Parameters	Value	Normal value
Haemoglobin	11.6 gm%	12-15 gm%
Total leukocyte count	12800	4000-11000 cells/ cu.mm
Platelet count	2.48	1.5- 4.1 lacs/ cu. mm
Mean corpuscular volume	82.5	83-101 fL
Alkaline phosphatase	130	38-126 U/L
Alanine aminotransferase	52	<35 U/L
Aspartate aminotransferase	47	14-36 mg/dL
Urea	21	15-36 mg/dL
Creatinine	1.1	0.52-1.04 mg/dL
Potassium	4.6	3.5-5.1 meq/L
Total bilirubin	1.3	0.2-1.3 mg/dL
Conjugated bilirubin	0.6	0-0.3 mg/dL
Creatine kinase- MB (Ck-MB)	11	<16 U/L
Troponin-I	6.13	<15 pg/mL
Prothrombin time	12.3	11.9 sec
Activated partial thromboplastin time	31.7	29.5 sec

[Table/Fig-2]: Laboratory investigations of the patient.

On consultation with the cardiologist, the patient was advised to withhold all the drugs, and the patient was planned for coronary angiography. Coronary angiography was normal. Beta-blocker and fluoxetine were withheld, and the patient was monitored with serial ECGs. Seventy-two hours after withholding his medications (metoprolol and fluoxetine), his heart rate was found to be 68 beats per minute, and his ECG was suggestive of RBBB with a heart rate of 64 per minute without features of CHB [Table/Fig-3].

Patient was shifted out of the cardiac ICU on day 3 to the general ward and was further monitored for two days. His antihypertension



[Table/Fig-3]: ECG of the patient after three days.

medication was switched to tablet telmisartan 40 mg once daily and tablet sertraline 25 mg once daily, and the patient was asked to follow-up after two weeks. In the follow-up, his ECG remained the same, and there were no fresh complaints.

DISCUSSION

Bradycardia is a common side effect of beta-blockers, non dihydropyridine calcium channel blockers, digoxin, amiodarone, and sympathomimetic antihypertensive drugs like clonidine [1]. Although there is a clear connection between depressive disorders and Cardiovascular Diseases (CVD), several facets of this connection have remained challenging. Upto 50% of people with Coronary Artery Disease (CAD) have some degree of depression, and 20% of them receive a Major Depressive Disorder (MDD) diagnosis [2].

On the other hand, it has been shown that depressed individuals are more likely to experience a myocardial infarction even when they have their cardiovascular risk factors well managed. Furthermore, patients with psychiatric conditions such as depression have a significantly increased risk of mortality from cardiovascular events [2].

Major depression is effectively managed through pharmacotherapy, especially in patients with chronic illnesses who often do not adhere to or respond to non pharmacological therapies [2]. Cardiovascular adverse events, in particular, are significant due to their debilitating and life-threatening nature. Even individuals without a history of cardiovascular issues can encounter severe complications, including arrhythmias or sudden cardiac death. Clearly, individuals with CVD are more prone to such adverse events, which could negatively impact the progression of their cardiac condition [2,3].

One of the most serious and significant adverse effects of antidepressants is arrhythmias. Through intricate processes involving voltage-gated sodium, potassium, and calcium ion channels in cardiac myocytes and the conduction system, various groups of antidepressants, particularly Tricyclic Antidepressants (TCAs), can cause different forms of arrhythmias [3]. Antidepressants are routinely recommended in medical settings; however, several negative effects on the cardiovascular system have been identified thus far. These include reduced cardiac conduction and output, arrhythmias, sudden cardiac death, bradycardia, tachycardia, hypertension, hypotension, orthostatic hypotension, ECG alterations, electrolyte abnormalities, hypertension, and tachycardia [2].

Examples of first-generation antidepressant drugs include Monoamine Oxidase Inhibitors (MAOIs), Tricyclic Antidepressants (TCAs), and atypical antidepressants. Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Norepinephrine Reuptake Inhibitors (SNRIs), and atypical antidepressants are examples of second-generation antidepressant drugs [2].

The earliest antidepressants used in clinical practice were MAOIs (Tranylcypromine, Phenelzine, Moclobemide, Selegiline, etc.). Although MAOIs are effective at reducing depression symptoms, a number of adverse side effects and medication interactions severely limit their clinical use. Cardiovascular adverse effects typically manifest 12 to 24 hours after MAOIs have reached their lethal levels because it takes time to establish such neurotransmitter disruptions. Hypotension and tachycardia are commonly reported under the influence of MAOIs; this phenomenon should be closely monitored in elderly patients who are more vulnerable to cardiovascular events [2,3].

Prior to the development of SSRIs, TCAs (Imipramine, Amitriptyline, Nortriptyline, Desipramine, Amoxapine, Clomipramine, Doxepin, Maprotiline, etc.) were the first-line treatment for depression. However, their use has been limited recently, primarily due to cardiovascular side effects. TCAs are still frequently used, especially when patients do not respond to SSRI therapy, even if they are not prescribed as often [2,4].

Despite having a positive therapeutic profile, SSRIs have fewer and milder adverse effects compared to other antidepressants. There is a significant anticholinergic impact and low cardiotoxicity between SSRIs and TCAs, which is the main distinction between the two. In fact, due to their lower side-effect profile and reduced toxicity following overdose, SSRIs are now prescribed more frequently than TCAs [4,5]. Because of their more favourable safety profile and wider margins of nontoxic levels compared to other antidepressant classes, SSRIs (Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline, Paroxetine, etc.) are typically the first-line antidepressant medications. At therapeutic levels, SSRIs are unlikely to cause cardiovascular adverse effects as they are generally mild. However, underuse of SSRIs has been associated with orthostatic hypotension, moderate bradycardia, and conduction abnormalities such as QT prolongation. Interestingly, it has been suggested that SSRIs may even positively impact the cardiovascular system through intricate pathways. By inhibiting serotonin uptake into platelets, SSRIs reduce the occurrence of ischemic cardiac events and interfere with platelet activation and aggregation [2,4].

SSRIs can lengthen QT intervals, but at therapeutic levels, they typically do not lead to life-threatening arrhythmias. In conclusion, SSRIs are unlikely to cause severe cardiovascular side effects when used within the approved dosage limits, but further research using prospective surveillance is needed to determine their exact cardiovascular safety profile [2,5].

Compared to TCAs, SSRIs significantly reduce the occurrence of anticholinergic, antihistaminergic, and cardiotoxic side effects. Bradycardia, orthostatic hypotension, and abnormalities in the electrical activity of the heart, such as prolonged QRS or QT intervals, are the most common cardiac adverse effects. SSRIs may also directly constrict blood vessels, leading to Prinzmetal's angina, a type of myocardial ischaemia. Furthermore, due to the vasoconstrictive effects of SSRIs, individuals who are more susceptible to haemorrhagic and vasoconstrictive disorders should use SSRI medication with extreme caution [5]. Some antidepressants like agomelatine [6,7], mirtazapine [8-10], and sertraline [11] are considered safe in CVDs.

Beta-blockers, which are class II anti arrhythmic drugs, are commonly used to treat cardiac disorders and primarily target the sinoatrial and AV nodes. They are the most prescribed cardiac drug for bradyarrhythmia [1]. Beta-blockers reduce sinus node automaticity by inhibiting sympathetic nervous system activity and promoting parasympathetic nervous system activity. Calcium and sodium currents are essential for the sinus node and AV node to generate action potentials. Ivabradine inhibits the cyclic nucleotide-gated funny channels (If) in the sinus node. While drug-induced bradycardia rarely results in death, torsades de pointes can occur when bradycardia and QT prolongation are present [3,8].

Metoprolol, a commonly prescribed cardioselective beta-blocker, undergoes significant O-demethylation, hydroxylation, and N-dealkylation metabolism in the liver. In-vitro studies have

shown that Cytochrome P450 2D6 (CYP2D6) predominantly mediates the hydroxylation of metoprolol and partially mediates the O-demethylation of the drug. Thus, approximately 70% of metoprolol's metabolism is mediated by CYP2D6. By inhibiting CYP2D6, SSRIs may inhibit the metabolism of metoprolol. Among SSRIs, paroxetine and fluoxetine are some of the strongest CYP2D6 inhibitors [2,4,10].

CONCLUSION(S)

Authors concluded that the complete heart block (CHB) observed in present patient was likely due to the co-administration of fluoxetine and metoprolol. Initially, the patient was asymptomatic while only receiving metoprolol therapy. However, after starting fluoxetine, the patient experienced chest heaviness and developed a complete AV block two months after initiation of fluoxetine treatment. Subsequently, complete recovery was observed upon discontinuing fluoxetine medication, whereas stopping metoprolol alone did not restore normal rhythm. Authors hypothesised that the synergistic effect of the beta blocker and fluoxetine may have contributed to this CHB. Various cardiovascular issues should be carefully evaluated in individuals who require antidepressant medication, based on multiple lines of evidence. It is particularly recommended to perform an ECG before and after initiating medication, especially in patients with pre-existing cardiac conditions and/or risk factors. Periodic ECG monitoring is also essential to detect any QT prolongation, arrhythmias, or other significant ECG abnormalities that indicate a higher risk of life-threatening conditions. It is crucial to consider the possibility that a patient's arrhythmia may have been triggered by medications.

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