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Bisoprolol induced Bradycardia: A Clinical Pharmacist intervention

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ABSTRACT:
Bisoprolol is a cardio-selective beta blocker approved by the United States Food and Drug Administration for the management of hypertension and congestive cardiac failure. This case report focuses on a 61-year-old female patient with a history of ischemic heart disease and hypertension who developed bradycardia as an adverse effect of bisoprolol. The patient initially presented with a recent episode of fever, and during her admission, bisoprolol was prescribed to further control her blood pressure on day 6. On day 7, the patient experienced bradycardia, which was promptly managed through continuous monitoring of her pulse rate. With vigilant monitoring and intervention, the patient's condition stabilized, and she was discharged in a stable state. This case highlights the importance of recognizing and managing potential adverse effects of bisoprolol, especially in patients with underlying cardiovascular conditions, emphasizing the need for individualized medication management and close monitoring to ensure patient safety.

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INTRODUCTION:

Bisoprolol, a Food and Drug Administration (FDA)-approved cardio-selective beta blocker, is widely used for the management and treatment of hypertension and congestive heart failure (CHF) [1]. It exerts significant effects on both cardiovascular and non-cardiovascular conditions [2]. Functioning as a cardio-selective inhibitor of beta 1-adrenoceptor, it lacks intrinsic sympathomimetic and membrane stabilizing activities within therapeutic dosages. Additionally, it exhibits beta 2-adrenoceptor inhibition and a negative chronotropic effect [3]. Consequently, bisoprolol reduces myocardial oxygen consumption and inhibits renin release in cells of the juxtaglomerular area [1]. With an oral bioavailability

of 80 to 94 % and approximately 30 % protein binding, it undergoes hepatic metabolism (50 %) and is predominantly eliminated unchanged through urine, with an elimination half-life of 9 to 12.4 h [3]. The notable adverse effects associated with bisoprolol include dizziness (10 %), insomnia (8 to 10 %), bradyarrhythmia (9 %), upper respiratory tract infection (5 %), diarrhea (4 %), rhinitis (4 %), arthralgia (3 %), cough (3 %), dyspnea (2 %), nausea (2 %), pharyngitis (2 %), sinusitis (2 %), vomiting (2 %), among others [4]. Thus, the central focus of this case study is to explore and emphasize the clinical significance of bradycardia, an adverse effect associated with the use of bisoprolol.

CASE REPORT:

A 61-year-old female with a known case of ischemic heart disease (IHD) and hypertension (HTN) presented with an 8-day history of fever, lasting for 2 days, characterized by intermittent high-grade fever without chills. The patient also complained of bilateral lower limb swelling and pain, which started suddenly and gradually progressed. The pain was relieved by taking analgesics. Additionally, she reported acute-onset swelling and localized pain in the wrist joint, which was localized and slowly progressive, with a non-radiating dull aching type of pain. There was no history of vomiting, loose stools, abdominal pain, burning micturition, chills, rigor, rashes, petechiae, yellowish discoloration of the eyes, giddiness, or weakness.

Table 1. Indication and dosing of Bisoprolol [3].

Bisoprolol (FDA Approval date: 31/07/1992)	
Indication	**Dosing**
FDA Labeled Indication	
Hypertension	Initial 2.5 to 5 mg orally once daily (OD), can be increased to 10mg or 20mg OD if needed Maximum Dose: 20mg/day
Non-FDA Labeled Indication	
Angina pectoris	5 to 20 mg orally OD
Congestive Heart Failure	Initially 1.25 mg orally OD Maximum Dose: 10 mg OD

The patient had a past history of IHD with percutaneous transluminal coronary angioplasty (PTCA) and stenting in the right coronary artery (RCA), as well as hypertension for which she was taking Tablet Rosagold 10 (Rosuvastatin + Aspirin + Clopidogrel) 10/75/75 mg 0-0-1 and Tab Telmi 20 (Telmisartan) 20 mg 1-0-0 (Table 1).

Laboratory investigation revealed chikungunya (Immunoglobulin M-IgM antibody) positivity and an elevated c-reactive protein (CRP) level of 13.9 mg/dL. The two dimensional-echocardiography (2D-ECHO) showed regional wall motion abnormalities (RWMA) and a grade I mitral valve regurgitation (MR), along with average chamber size, regular pulmonary artery (PA) pressure, concentric left ventricular hypertrophy (LVH), and a left ventricular ejection fraction (LVEF) of 50 %. Treatment given during hospital admission is summarized in Table 2.

On Day 5 of admission, in view of high blood pressure (170/80 mmHg) during evening rounds, the patient was advised with a Tablet Bisoprolol 2.5 mg 1-0-0. On Day 7, during morning pre-rounds and rounds, the patient was found to have bradycardia (56 and 54 bpm) (Fig 1). When the medications given were evaluated for the cause of bradycardia, the culprit drug was found to be bisoprolol.

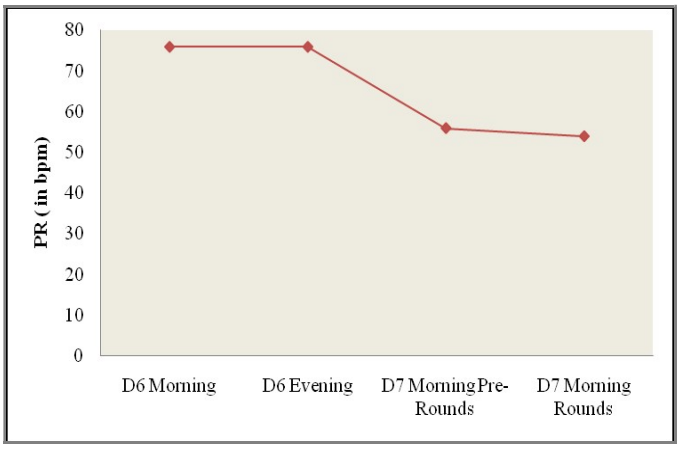

Fig 1. Pulse rate on Day 6 and 7 of admission.

CAUSALITY ASSESSMENT:

Causality assessment of the relationship between the drug and the adverse effect was conducted using the Naranjo Adverse Drug Reaction Probability Scale and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment Scale. Based on these assessments, the adverse drug reaction (ADR) was categorized as "Possible" (Table 3). The severity of the ADR was determined using the Modified Hartwig and Siegel Severity Assessment Scale, which indicated a severity of level 2.

DISCUSSIONS:

Beta-blockers such as bisoprolol inhibit adrenaline and noradrenaline from binding to beta-adrenoceptors in specific areas of the body. This blocks a stimulation that would otherwise cause the heart to beat, lowering the

Table 2. Treatment given during admission.

Sl. No.	Generic Name	Dose	Frequency	Duration in days						
				D 1	D 2	D 3	D 4	D 5	D 6	D 7
1	Tab. Telmisartan	20 mg	1-0-0	√	√	√	√	√	√	√
2	Tab.Rosuvastatin+Aspirin+Clopidogrel	10/75/75 mg	0-0-1	√	√	√	√	√	√	√
3	Inj. Ceftriaxone+Salbactum	1.5 g	1-0-1	√	√	√	Stopped			
4	Inj. Pantoprazole	40 mg	1-0-0	√	√	√	√	√	√	√
5	Cap. Doxycycline+Lactobacillus	100 mg/5 billion spores	1-0-1	√	√	√	√	√	√	√
6	Inj. Dexamethasone	8 mg	1-0-0	√	√	√	√	√	√	√
7	Inj. Normal saline with 1 ampule Multivitamin	@50 ml/h	0-1-0	√	√	√	Stopped			
8	Tab. Calcium+Vitamin D3+Methylcobalamin+L-Methylfolate+Calcium+Pyridoxal-5-Phosphate	1250 mg/500 mg/2000 I.U./1500 µg/1mg/20mg	0-1-0	-	-	√	√	√	√	√
9	Inj. Cefoperazone+Salbactum	3 g	1-0-1	-	-	√	√	√	√	√
10	Tab. Etoricoxib+Paracetamol	60 mg+325 mg	1-0-1	-	-	-	-	√	√	√
11	Aceclofenac+Paracetamol gel		1-1-1	-	-	-	-	√	√	√
12	Tab. Bisoprolol	2.5 mg	1-0-0	-	-	-	-	-	√	√
13	Tab. Lactic acid bacillus	120 million spores	1-1-1	-	-	-	-	-	√	√
14	Tab. Amlong	10 mg	Stat	-	-	-	-	-	-	√

Table 3. Causality Assessment of Adverse Drug Reaction (ADR).

ADR	Naranjo's Scale	WHO-Causality Scale	Severity
Bradycardia	Total Score 3: **Possible**	**Possible**: Event with reasonable time relationship to drug intake, could also be explained by disease or other drugs, information on drug withdrawal is lacking.	Level 2: The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in length of stay.

heartbeat and decreasing the force with which blood flows through the body [5].

The Cardiac Insufficiency Bisoprolol Study II (CIBIS II) demonstrated that adverse effects such as dizziness, bradycardia, hypotension, and fatigue occurred more frequently in bisoprolol-treated patients compared to those receiving placebo, regardless of medication causality [6]. Conversely, only one patient in the elderly group experienced bradycardia, a side effect associated with bisoprolol, according to research by Haneda S, *et al.* Given these findings, bisoprolol is a safe and effective antihypertensive medication for individuals with essential hypertension, irrespective of their age [7]. Another study by Ilkeda, *et al*. highlighted the beneficial and effective antihypertensive properties of bisoprolol, with bradycardia being the most commonly observed adverse effect [8]. While electrocardiograms (ECGs) play a significant role in identifying and managing bradycardia, simple methods such as palpating the patient's pulse or listening to heart sounds can also be sufficient for detecting abnormally slow heart rates and initiating emergency treatment [5].

CONCLUSION:

Bisoprolol has shown effectiveness in managing hypertension; however, it is important to note that bradycardia is a commonly observed adverse effect in some patients. When bradycardia occurs due to bisoprolol, close monitoring is crucial, and in most cases, no further management may be required. However, in cases of severe bradycardia, discontinuing bisoprolol and

considering alternative antihypertensive medications may be necessary. This emphasizes the need for standardized monitoring protocols and individualized approaches to optimize patient safety and ensure appropriate management of adverse effects associated with bisoprolol therapy.

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