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A Case Series on Serious Adverse Drug Reactions Caused by Carvedilol

Alwy Joseph [1], Manish Mohan M [2], S K Mathew [2*], Neenu Chandrasekhar [3], Swetha Reba Mathewes [3]
[1,2&3]Department of Pharmacology, [2*]Department of Medicine,
Believers Church Medical College, Thiruvalla

***Corresponding Author:**
Manish Mohan M
Department of Pharmacology, Believers Church Medical College, Thiruvalla

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Abstract
Carvedilol is a non-selective adrenergic blocker that is widely used to treat heart failure with reduced ejection fraction (HFrEF), hypertension, and left ventricular dysfunction after a heart attack (MI). Due to its use in patients who usually have multiple comorbidities, it is critical to understand the possible serious adverse drug reactions (ADR). In this case series, we describe three important ADRs of carvedilol which have been reported to the ADR monitoring centre (AMC) at our institution.

Keywords: Carvedilol, Adverse drug reaction, Adrenergic blockers

Introduction

Adrenergic receptor (AR) antagonist carvedilol blocks a variety of AR types. In particular, it blocks ARs in the vasculature and works as an inverse agonist at the alpha and beta-ARs, which causes vasodilation. As this AR type is by far the most prevalent in adult human myocardium (both failing and non-failing), it is comparatively specific in the heart. It can offset the negative effects of the sympathetic hyperstimulation that goes along with and aggravates chronic heart failure since it blocks nearly all ARs in the body (except beta receptors. [1]. It is a relatively well-tolerated drug with fewer adverse effects than other beta-blockers, and adverse effects are dose-dependent. The most common adverse effect associated with carvedilol is undesired, excessive hypotension secondary to its vasodilating properties. These include dizziness, lightheadedness, fatigue, and headaches. It also causes adverse effects that are related to its beta-blocking properties, such as dyspnea, bronchospasm, bradycardia, malaise and asthenia. [2]. Here we elaborate on three cases which demonstrate serious and probably preventable ADR of this drug.

Case Study

Case 1- Carvedilol Induced Hypotension

A 67-year-old lady presented to the outpatient department, complaining of generalised weakness. She had Type 2 diabetes mellitus, coronary artery disease, and acute kidney injury. She was on several oral medications, which included, glyburide 1gm BD (twice daily), carvedilol 25 mg BD, trimetazidine 35 mg BD, spironolactone 25 mg BD, sodium bicarbonate 500 mg TID (three times daily), and probiotics OD (once daily). It was observed that after starting the tablet carvedilol 25 mg BD, the patient developed symptoms of hypotension, and blood pressure was recorded as 80/60 mmHg during evaluation. The drug was stopped, and on subsequent visits, her blood pressure was recorded as 110/70 mm Hg, and the patient was found to have symptomatic improvement as well.

Case 2- Carvedilol-Induced Acute Kidney Injury

A 55-year-old lady with chronic liver disease, systemic hypertension, and type 2 diabetes mellitus, presented with a history of abdominal distention,

pedal edema, and reduced appetite in the last five days. Her medication history included tablet cilnidipine 10 mg BD, Inj. human mixtard s/c, tablet carvedilol 3.125 mg BD, and once daily probiotics. She was found to have acute kidney injury and her serum creatinine level was 2.46 mg/dl at presentation, the value rising to 2.55 mg/dl and thereafter to 2.66 mg/dl during admission in the hospital. Carvedilol was suspected as the offending agent and was discontinued, following which her serum creatinine value improved.

Case 3 - Carvedilol Induced Bronchospasm

A 67-year-old lady was hospitalized with bronchospasm and dyspnea. She had type II diabetes, chronic liver disease, and hypertension. She was on tablet carvedilol 6.25 mg BD and ursodeoxycholic acid tablets 150 mg BD. She gave a history of shortness of breath since starting carvedilol; hence, the drug was discontinued. Following dechallenge of the drug, the patient's symptoms improved and she could be discharged from the hospital.

Case Number	Causality	Type of adr	Severity	Seriousness	Preventability	Outcome
1	Probable	A	Level 3	Life threatening	Definitely preventable	Recovering
2	Probable	B	Level 4	Hospitalisation initial/ prolonged	Probably preventable	Recovering
3	Probable	A	Level 3	Hospitalisation initial/ prolonged	Definitely preventable	Recovered

Discussion

Carvedilol and other beta blockers produce effects dependent on the dosage and characteristics of the patient [3]. They may be more harmful to the cardiovascular system. The majority of the adverse effects are severe and preventable [4]. Hence It is necessary to decrease medication administration frequency and prevent concurrent use of other medications that lower heart rate with carvedilol and most of the time the patient experiences the psychological effect of being given incorrect or incomplete drug information [5]. The patients in our study are mostly elderly. Hence, careful monitoring is essential when taking Carvedilol especially if there are signs and symptoms suggestive of an ADR.

Case number 1 is an example of carvedilol-induced hypotension. Hypotension accounts for approximately 3.5% of all cases reported to the Uppsala Monitoring Centre (UMC) under the World Health Organization (WHO) initiative for worldwide drug monitoring [6]. This case of carvedilol-induced Bradycardia (WHO –UMC ID: IN- IPC -300731979), was reported by our AMC. The causality was determined as probable using the WHO-UMC causality assessment scale, the type of ADR was determined to be type A (augmented ADR) using the Rawlins-Thompson classification, and the seriousness was assessed using WHO criteria to be "life-threatening". The severity was assessed by Modified Hartwig's scale and was found to be level 3, and the outcome of the reaction was determined by WHO criteria as "recovering." The ADR was found to have been preventable according to the Schumock and Thornton Scale.

Case number 2, depicts an acute kidney injury caused by carvedilol. Renal and urinary problems account for around 2% of carvedilol-related ADR, one-fourth of which are cases of acute kidney injury [6]. The WHO-UMC ID of this report filed by our AMC was IN-IPC- 300780195. The causality was determined to be probable using the WHO-UMC causality assessment scale, the type of ADR was assessed to be Type B (Bizarre ADR) using the Rawlins-Thompson classification, the seriousness was determined using WHO criteria as "hospitalisation initial/prolonged," and the severity was defined by Modified Hart wig's

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scale to be level 4 severity. The outcome of the reaction was determined using WHO criteria as "recovering." The reaction was found to have been probably preventable according to the Schumock and Thornton Scale.

Case number 3, shows bronchospasm induced by Carvedilol. Respiratory ADR accounts for approximately 6% of all carvedilol-related ADR reported to the WHO-UMC, out of which 3.4% are cases of bronchospasm [6]. The WHO-UMC ID of this report submitted by our AMC was IN-IPC-300662677. The causality was determined to be probable using the WHO-UMC causality assessment scale, the type of ADR was found to be Type A (Augmented ADR) using the Rawlins-Thompson classification, the seriousness was determined using WHO criteria as "hospitalisation initial or prolonged," the severity defined by Modified Hartwig's scale was at level 3. The reaction's outcome was determined by the WHO criteria as "recovered.". The reaction was observed to be definitely preventable according to Schumock and Thornton Scale.

Conclusion

This case series demonstrates that carvedilol should be used with caution, particularly in the elderly, who have multiple comorbidities and metabolic risk factors.

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