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CASE REPORT

Drug-drug interactions presenting as Bradyarrhythmia and Hyperkalaemia: A Case Report

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ABSTRACT

Introduction: Drug-drug interactions can be the major negative consequence while using a multidrug treatment approach. Hypertension is one of the preventable causes of cardiovascular disease. Treatment of hypertension is individualized based on the patient's condition. Some patients may require simultaneous treatment with 4 to 5 anti-hypertensive drugs.

Case Details: We are presenting a case of a 69-year-old female patient, receiving 4 classes of antihypertensive drugs. The patient was admitted to our hospital with hyperkalemia and bradyarrhythmia. The patient had a history of being treated with Atenolol, Losartan, Hydrochlorothiazide, and Diltiazem. Hyperkalaemia observed in this patient can be attributed to Losartan and Atenolol. Bradyarrhythmia can be the result of drug interaction between Diltiazem and Atenolol.

Conclusion: Physicians should always keep in mind the interactions and adverse effects caused by medications used in the treatment of Hypertension.

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Introduction

Around 26% of all adverse events are caused by Drug-drug interactions (DDI) (McQuade et al., 2021). Hypertension (HTN) is one of the preventable causes of cardiovascular disease, which can be defined as systolic blood pressure (BP) > 140 mm Hg and/or diastolic BP > 90 mm Hg (Mills et al., 2020). Depending on epidemiological conditions, comorbidities, side effects, and variations in response to antihypertensive drugs, the treatment strategy has to be individualized (Brunton LL, 2018). Usually, patients are prescribed more than one anti-HTN to bring their BP within the target range. Combinations provide synergistic effects (beneficial effects), but an anti-HTN combination should be rationally chosen to avoid the occurrence of unwanted DDI.

Here, we are presenting a case of a 69-year-old female patient with, a known case of hypertension for the last 15 years, having a history of being treated with four different classes of antihypertensive drugs, admitted to the hospital with suspected ADRs of Bradyarrhythmia and hyperkalemia.

Case Details

A 69-year-old female patient was brought to our tertiary care hospital with chief complaints of difficulty in breathing for 7 days, abdominal pain and diarrhea for 7 days, decrease urine output for 3 days, pedal edema, and, 2 episodes of vomiting.

The patient was relatively asymptomatic 7 days before the admission. Then she started complaining of breathlessness

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on exertion and pedal edema and was treated by her family physician for the same with symptomatic treatment. Afterward, she developed diarrhea and abdominal pain, which was dull and aching in nature with mild to moderate severity and incomplete evacuation of the bowel. It was managed with symptomatic treatment. The day before admission, the patient experienced breathlessness even with rest, and this brought the patient to our hospital.

The patient was a known case of Hypertension and type-II Diabetes for 15 years, and dyslipidemia for 5 years. She had been taking a tab. Fenofibrate 145 mg, tab. Losartan + Hydrochlorothiazide 145 mg, tab. Amlodipine + Atenolol 2.5/50 mg, tab. Losartan 50 mg, tab. Diltiazem 30 mg and tab. Metformin 500 mg.

On the day of admission, her vitals were:: Temp. was normal, Pulse- 42/min, B.P.- 160/70 mm Hg, Oxygen saturation- 94% on room air, and Respiratory Rate 24 per minute. Her Random Blood sugar was 222 mg/dl. The ECG of the patient on admission is presented in **Figure 1**.

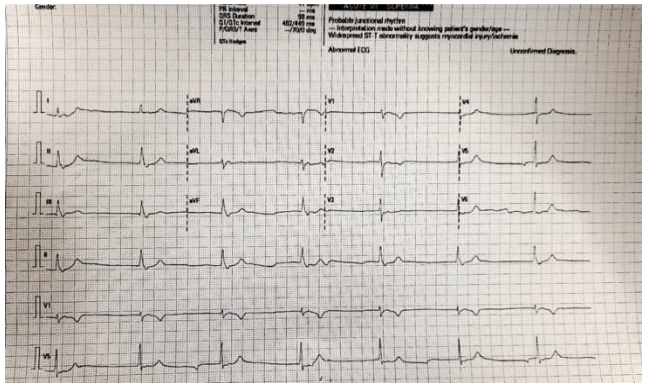


Figure 1: ECG of the patient on admission.

Her lab investigation revealed Haemoglobin –8.5 g/dL, Total W.B.C.– 8.39 KU/L, Total platelet count- 287 KU/L, S. Creatinine-2.39 mg/dL, S. Sodium- 120 mmol/L, S. Potassium-7.17 mmol/L, S. chloride- 99 mmol/L, Blood Urea- 79.5 mg/dL, Procalcitonin- 81.36 ng/mL, CRP-146.55 mg/L, S.G.P.T.-50 U/L. The data has been presented in **Table 1**.

Table 1: Lab. Investigations of Patient during Admission

	05/08	06/08	07/08	08/08	09/08	10/08	12/08
Hemoglobin (g/dL)	8.5		9.3			9.2	
WBC (10^6/uL)	8.39		10.18			8.85	
Platelet count (ku/L)	287		301			338	
Blood urea (mg/dL)	79.5		65.8	73		62	
Creatinine serum(mg/dL)	2.39		1.75	2.09		1.53	
Sodium serum (mmol/L)	120	126		130		119	119
Potassium serum(mmol/L)	7.17	6.75	5.68	4.8	4.93	4.76	4.62
Chloride serum (mmol/L)	99						
Calcium -serum (mg/dL)	9.0	9.6					
SGPT(alt) (u/L)	50						
Uric acid serum (mg/dL)		11.17					
Phosphorous - serum (mg/dL)		5.67					

Urine analysis revealed the presence of a few pus cells and glucose in the urine sample.

USG of the Abdomen -Pelvis revealed increased cortical echogenicity of both kidneys with maintained cortico-medullary differentiation, suggestive of chronic kidney disease and small obstructive calculus in the lower pole calyx of the right kidney.

The patient was diagnosed as a case of Bradyarrhythmia by the treating physician and was treated with IV Atropine. This could be attributed to the additive action of Diltiazem and atenolol to cause bradycardia. This ADR has been reported under the unique ID number IN-IPC-30661702 to the Indian Pharmacopoeia Commission. As the reaction follows a temporal relationship and can also be explained by other drugs, causality assessment of this ADR is "Possible".

She also presented with hyperkalemia, for which she was started on an IV Glucose-Insulin (GI) drip, Calcium Gluconate, and Furosemide to correct her hyperkalemia. This ADR has been reported under the unique ID number IN-IPC-30661131 to the Indian Pharmacopoeia Commission. The causality assessment of this ADR is "Possible".

All the suspected drugs were withdrawn. After 8 days of admission, the patient's condition improved, Heart Rate was 66/ minute, no complaints of breathlessness. S. creatinine level was found to be on decreasing trend, and K+ levels were within range; hence the de-challenge was positive. The data has been presented in **Figure 2**.

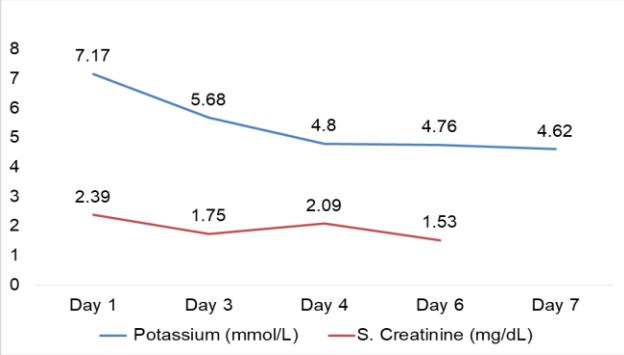


Figure 2: S. Potassium and S. Creatinine levels on follow-up during admission.

Subsequently, she was discharged with the following medications: tab. Clopidogrel 75 mg, tab. Atorvastatin 20 mg, tab. Febuxostat 40 mg, tab. Teneligliptin 20 mg, tab. Dapagliflozin 10 mg, tab. Torsemide 10 mg, tab. Sevelamer Carbonate, tab. Tolvaptan 15 mg, tab. Sodium Bicarbonate 500 mg TDS and other symptomatic treatment.

Discussion

Hypertension is the most common cardiovascular disease, which acts as a major risk factor for other cardiovascular diseases, such as stroke, coronary artery disease, and myocardial infarction. Apart from control of blood pressure, the goal of antihypertensive treatment is directed to reduce morbidity and mortality from other cardiovascular diseases (Brunton LL, 2018).

Classification of antihypertensive agents is based on their sites or mechanism of action. The current treatment strategy involves the simultaneous use of different classes of antihypertensives for synergistic effects while reducing dose-related adverse effects (Brunton LL, 2018). But it can also lead to potential drug-drug interactions between them.

In the above-mentioned case, the patient was being treated with a combination of Angiotensin Receptor Blocker (ARB) and Diuretic (Losartan + Hydrochlorothiazide), Calcium Channel Blocker (CCB) (Diltiazem & Amlodipine), and β-blocker (Atenolol).

The non-dihydropyridine subclass of CCB, which include Diltiazem, has inhibitory effects on the sinoatrial (SA), and atrioventricular (AV) nodes, ultimately resulting in slowed cardiac contractility and conductivity. Another subclass, Dihydropyridines, including Amlodipine, has a major direct effect on peripheral vasodilation (McKeever et al., 2022).

Mechanisms by which β-blockers lowers blood pressure comprise decreased cardiac output due to a decrease in heart rate and contractility, inhibition of renin release, and central nervous system effects (Fauci et al., 2018).

Simultaneous use of β-blockers with CCB like Diltiazem can enhance the negative chronotropic effects of the latter, leading to bradyarrhythmia and ultimately Heart Block (Fauci et al., 2018). In toxic doses, Diltiazem alone can cause atrioventricular conduction abnormalities, complete heart block, and idioventricular rhythm (McKeever et al., 2022).

In our case, to combat her increased blood pressure, the patient had been treated with Diltiazem and β-blocker like Atenolol concurrently. Interaction between these two drugs could be the possible reason for bradyarrhythmia, which the patient suffered.

Also, Angiotensin Receptor Blockers are a well-known cause of drug-induced hyperkalemia. It can be enhanced with factors such as underlying renal disease or drugs like β-blockers (Brunton LL, 2018). On admission, our patient had a serum potassium level of 7.17 mmol/L, which can be attributed to losartan and atenolol. After lab. and radiological investigations she was found to be suffering from chronic kidney disease, which can also alter potassium homeostasis.

Conclusion

Drug-drug interactions could be one of the major concerns while concurrently using 2 or more classes of drugs for the treatment of hypertension. The physician should always be aware of adverse effects arising out of unwanted DDI. They should readily use an online DDI checker as well as standard pharmacology textbooks before prescribing and dispensing medications. With the prolonged comorbid condition, when the disease gets decompensated due to effects on the kidney, some drug modification may be required. Regular monitoring of symptoms and laboratory investigations may help to prevent such life-threatening complications.

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