Bradyarrhythmic Cardiac Arrest—A Rare Manifestation of Fexofenadine Cardiotoxicity

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Abstract
A 66-year-old diabetic, hypertensive, and hypothyroid female presented in the emergency department with cardiac arrest, for which cardiopulmonary resuscitation was immediately initiated. She had been on oral fexofenadine for 36 h prior to the event. Post successful resuscitation, her cardiac rhythm showed high-grade atrioventricular block. Patient was treated with mechanical ventilatory support and temporary transvenous pacing. No treatable cause could be identified, and she recovered completely following fexofenadine discontinuation, without need for a permanent pacemaker. She has remained asymptomatic during 1 year of follow-up with no documented arrhythmias. An electrophysiological study at 6 months revealed prolonged HV interval (70 ms) with 1:1 AV conduction and no inducible arrhythmias. This is probably the first reported case of fexofenadine-induced cardiac arrest in a patient without previous history of heart disease.

Keywords:
Antihistamine cardiotoxicity, fexofenadine, high-grade AV block, drug-induced cardiac arrest, adverse drug reaction

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List of Abbreviations

| Abbreviation | Description                  |
|--------------|------------------------------|
| AH           | Atrio-hisian                 |
| AV           | Atrioventricular             |
| CPR          | Cardiopulmonary resuscitation|
| CSNRT        | Corrected sinus node recovery time |
| ECG          | Electrocardiogram            |
| EPS          | Electrophysiological study   |
| hERG         | Human Ether-à-go-go-Related Gene |
| HV           | His-ventricular              |
| K+           | Potassium                    |
| LAFB         | Left anterior fascicular block |
| LBBB         | Left bundle branch block     |
| LV           | Left ventricle               |
| RBBB         | Right bundle branch block    |

Introduction
Antihistamine medications are commonly prescribed to patients with allergic conditions. Current generation antihistaminics have the advantage of fewer side effects and a longer duration of action. Fexofenadine is a third generation, nonsedating oral antihistaminic with peak plasma concentration occurring 2 to 3 h after an oral dose and a duration of action of 12 to 24 h. It has an elimination half-life of 11 to 15 h. Being an active metabolite of terfenadine, but without the risk of QT prolongation, it is a frequently prescribed medication. Previous studies assessing safety of fexofenadine have reported that a single dose of 800 mg per day or multiple doses up to 690 mg twice daily in healthy volunteers did not produce any adverse cardiac events. We report an extremely rare case of fexofenadine-induced bradyarrhythmic cardiac arrest that recovered following drug discontinuation.
Case Report

A 66-year-old female with past medical history of diabetes mellitus, hypertension, dyslipidemia, and primary hypothyroidism was brought to the emergency department in cardiac arrest. She had had sudden syncope while at home after having dinner. There was no prior history of any cardiac ailment. Her previous medications included glimepiride, levothyroxine, and atorvastatin which she had been taking regularly. For recent upper respiratory tract infection associated coryza and pharyngitis, she had taken tablet fexofenadine 180 mg, 3 doses in preceding 36 h, prior to presentation. On examination, the patient was unresponsive, with unrecordable pulse and blood pressure. Cardiopulmonary resuscitation (CPR) was immediately initiated according to established protocols with resultant return of spontaneous circulation after 10 min of resuscitative efforts.

Post-resuscitation, her pulse rate was 30/min, regular with a blood pressure of 120/60 mm Hg. No murmurs were audible on cardiac examination. ECG demonstrated high-grade atrioventricular (AV) block with 4:1 AV conduction (Figure 1) and left bundle branch block (LBBB) morphology (QRSd: 144 ms, QT_C: 415 ms). Blood chemistry was suggestive of mixed acidosis with pH: 6.96, bicarbonate: 13.7 mmol/L, lactate: 10.4 mmol/L, serum potassium (K+): 4.45 mEq/L, and serum creatinine: 1.45 mg/dL. There was no evidence of hypoglycemia and thyroid function test was normal. Initial set of cardiac enzymes following CPR was raised with no subsequent rise on serial evaluation. Patient was immediately shifted to cath lab where a temporary transvenous pacemaker was inserted.

A coronary angiogram was performed which revealed normal coronaries. Noncontrast computed tomography of head revealed no abnormality. Subsequently, the patient was managed in intensive care unit on mechanical ventilatory support. Echocardiogram revealed concentric left ventricular (LV) hypertrophy, normal LV systolic function, and grade I LV diastolic dysfunction with no wall motion abnormality. Right-sided chambers showed no structural or functional abnormalities. Cardiac valves and pericardium were normal. Infectious disease screening tests were negative.

On the next day, ECG revealed sinus rhythm (Figure 2), 1:1 AV conduction with right bundle branch block (RBBB), left anterior fascicular block (LAFB), and first-degree AV block (heart rate: 100/min, QRSd: 120 ms, QT_C: 465 ms). Her biochemical parameters showed continued improvement (pH: 7.37, bicarbonate: 22.5 mmol/L, lactate: 1.2 mmol/L), following which she was extubated. ECG on day 3 (Figure 3) showed sinus rhythm with LAFB and first-degree AV block (heart rate: 80/min, QRSd: 103 ms, QT_C: 439 ms). Cardiac magnetic resonance imaging was done, which ruled out any structural heart disease. A 24-h holter study revealed no episodes of bradyarrhythmia, following which temporary pacemaker support was withdrawn. Thereafter, patient had an uneventful hospital stay and was discharged from hospital in an ambulatory state.

**Figure 1.** ECG post-resuscitation showing high-grade AV block with 4:1 AV conduction and LBBB morphology of QRS complexes.

**Figure 2.** ECG after 24 h, showing sinus rhythm, 1:1 AV conduction with RBBB, LAFB, and first-degree AV block.

**Figure 3.** ECG on third post-admission day demonstrating sinus rhythm, 1:1 AV conduction, LAFB, and first degree AV Block.
Patient was followed up on outpatient basis at 1 week, 1 month, and for 3 monthly intervals thereafter. At 1 week, LAFB persisted with first-degree AV block, with no fresh complaints of syncope/presyncope. At 6 months, ECG findings (Figure 4) were unchanged, and the patient continued to remain asymptomatic. She underwent a cardiac electrophysiological study (EPS) at 6 months, which revealed normal corrected sinus node recovery time (CSNRT) and atrio-hisian (AH) intervals while his-ventricular (HV) interval was prolonged: 70 ms (Figure 5), with 1:1 AV conduction on programmed electrical stimulation. Physiologic AV and ventriculoatrial wenckebaching occurred on pacing of right atrium and right ventricle respectively, with no inducible supraventricular or ventricular tachyarrhythmias. During 1 year of follow-up, patient has remained asymptomatic with no documented cardiac arrhythmias.

Discussion

Cardiovascular safety concerns with both first- and second-generation antihistaminics have been well documented previously. However, the major manifestations have been ascribed to prolongation of QT interval due to inhibition of Ikr K+ channel (hERG), leading to tachyarrhythmias. In comparison, bradyarrhythmias have rarely been documented with these drugs.

Our patient had taken 3 doses of fexofenadine 180 mg over a 36-h period. The timeline of development of arrhythmia coincided with intake of this drug. There was no evidence of structural heart disease, ischemia, electrolyte, or thyroid abnormalities that could have contributed to her clinical presentation. High-grade AV block with features of trifascicular block on subsequent ECGs, suggests a pan-conduction defect due to fexofenadine. After discontinuation of the drug during hospital stay, patient had sequential improvement in conduction abnormalities, consistent with weaning-off effects of the drug (4-5 half-lives). An EPS was not considered initially in view of rapid and sustained improvement in cardiac rhythm, with no bradyarrhythmia on holter monitoring.

A follow-up EPS at 6 months was performed, as repeated noninvasive evaluations did not reveal any episode of bradyarrhythmia, and the electrophysiological mechanism involved in such a dramatic initial presentation remained elusive. We also wanted to ascertain whether the patient was a candidate for permanent pacemaker implantation. EPS revealed infrahisian conduction abnormality with prolonged HV interval of 70 ms but did not warrant permanent pacemaker implantation in view of 1:1 AV conduction with pacing protocols and asymptomatic status of the patient. Our patient may have had a pre-existing latent infrahisian conduction disease (sclerodegenerative), which became manifest with fexofenadine intake. Another possibility is a new onset conduction system disease induced by fexofenadine, which has been recovering ever since with drug discontinuation.

The mechanism contributing to bradyarrhythmia with fexofenadine is unknown. Some studies suggest that it may prolong repolarization and induce ventricular arrhythmias/bradycardia or cause quinidine like effects by blocking a delayed rectifier current. All reported bradyarrhythmic events with fexofenadine have occurred with drug intake in preceding few hours to 2 weeks before the event, as in our patient.

Another important factor to consider is prior intake of atorvastatin, which is known to interact with p-glycoprotein. This protein is responsible for gastrointestinal clearance of fexofenadine and drug interaction could have led to increased serum concentration of this molecule. Of the 14 documented cases of bradyarrhythmias reported with fexofenadine, only 1 patient had history of concomitant atorvastatin intake. Hence, further studies are required to elucidate the exact
mechanism of toxicity and contributing drug interactions with fexofenadine.

Probability of adverse drug reaction is estimated using various causality algorithms which are described in detail elsewhere.\textsuperscript{11,12} World Health Organization-Uppsala Monitoring Centre causality assessment and Naranjo adverse drug reaction probability scale are the most widely used to report adverse drug reactions. Our case qualifies as Certain/Probable adverse drug reaction.\textsuperscript{11} Drug rechallenge was not considered in view of ethical concerns of inducing a serious cardiac complication in a patient who had otherwise recovered and become asymptomatic. To our knowledge, this is the first reported case of fexofenadine-induced cardiac arrest with successful recovery following drug discontinuation.

### Conclusion

Antihistamine medications may be associated with bradyarrhythmia. Newer generation drugs like fexofenadine have a better safety profile compared to earlier generation antihistaminics. However, the risk of bradyarrhythmia must be considered while prescribing these medications especially in high-risk groups such as elderly patients, asymptomatic patients with baseline conduction abnormalities, and patients on medications interacting with antihistaminics.

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