Case Report

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Internal Medicine Section

From Anaphylaxis to Arrhythmia: A Case Report of Fexofenadine-induced Bradyarrhythmia

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ABSTRACT

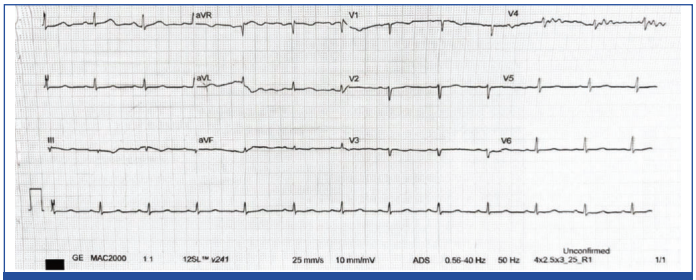
Anaphylaxis is a rapid, potentially fatal systemic hypersensitivity reaction, with adrenaline recommended as first-line treatment, followed by beta-2-agonists, glucocorticoids, and antihistamines. H1-antihistamines play a limited role but help relieve skin symptoms; undue side effects, such as sedation decrease with newer generations. Fexofenadine, a third-generation antihistamine, is preferred for its non-sedative profile and lack of anticholinergic or adrenergic effects. It reaches peak plasma levels in 2-4 hours, lasts 12-24 hours, and is 60-70% protein-bound with a half-life of 11-15 hours. As a terfenadine metabolite, it avoids QT prolongation and is considered safe. This is a rare case of sinus bradycardia following fexofenadine use in a 35-year-old female with no known comorbidities, who presented with angioedema and anaphylactic shock after taking cefixime and aceclofenac. She was stabilised with intravenous hydrocortisone and intramuscular adrenaline, then admitted to the Intensive Care Unit (ICU). Fexofenadine 180 mg twice daily and hydrocortisone 100 mg thrice daily were initiated. After three doses of fexofenadine, the patient developed worsening bradycardia, with a lowest recorded heart rate of 30 bpm. No other triggers were identified. Fexofenadine was discontinued, and symptomatic treatment included atropine and oral orciprenaline. Her heart rate stabilised without requiring pacing. Bradycardia resolved within three days of stopping fexofenadine, and orciprenaline was discontinued. The patient was discharged after a week. This case highlights a rare but significant adverse effect of fexofenadine, a commonly prescribed antihistamine. Clinicians should be aware of its potential to cause bradyarrhythmia and exercise caution when prescribing, especially in acute care settings.

Keywords: Antihistamine, Bradycardia, Drug-related side effects and adverse reactions, Good health and well-being

CASE REPORT

This case is reported after obtaining IRB approval (Approval number: CSP-MED/25/NOV/122/294). A 35-year-old lady with a sudden onset of giddiness and difficulty in breathing, in the early hours of the day, consulted at a local clinic where she was diagnosed to have anaphylactic shock, for which injection Adrenaline 1 mg IM, Injection Dexamethasone 4 mg i.v. and injection Chlorpheniramine i.v. were given and the patient was then referred immediately to the tertiary care centre in view of persistent hypotension. On arrival at the Emergency Department, the patient was dyspnoeic, had no complaints of chest pain or palpitations. The patient had developed a voice change and itching all over the body. She had no prior comorbidities, known drug allergies or history of syncope, atopy and prior anaphylaxis. Her vitals showed a blood pressure of 80/50 mmHg, pulse rate of 98/min, SpO2 98% in room air and respiratory rate of 28/min. On auscultation, the patient had scattered expiratory polyphonic wheeze. Injection Adrenaline 1 mg in 1:1000 dilution was given intramuscularly along with injection hydrocortisone 100 mg intravenously and 500 mL normal saline was rushed, following which her blood pressure improved to 110/70 mmHg. Upon reviewing her medical history, the patient informed that she had taken oral cefixime 200 mg and aceclofenac for left foot swelling the night prior to the development of symptoms. Patient was transferred to the intensive care unit and continued with injection of hydrocortisone 100 mg i.v. thrice daily and started on oral Fexofenadine 180 mg twice daily on the same day of admission (day 1) along with maintenance i.v. fluids. [Table/Fig-1] shows the electrocardiogram taken upon receiving the patient in the emergency department.

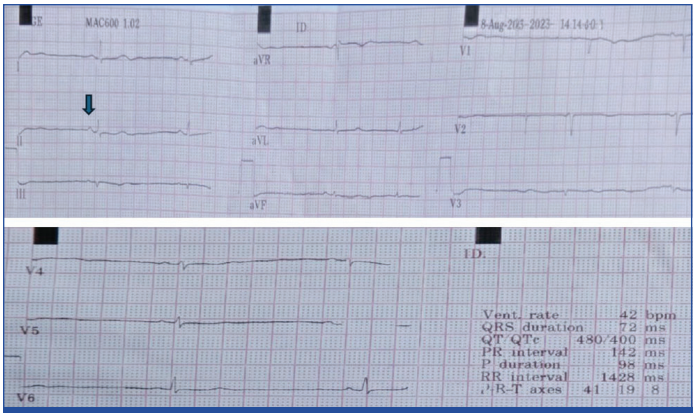
The next morning, the patient developed asymptomatic bradycardia and the lowest heart rate recorded was 45/min. [Table/Fig-2] shows an Electrocardiogram (ECG) taken at the time of bradycardia, displaying sinus bradycardia with no ST segment changes or T wave



[Table/Fig-1]: Twelve-lead electrocardiogram showing normal sinus rhythm taken at the time of presentation. The heart rate is approximately 90 beats per minute, with a narrow low-voltage QRS complex, a normal PR and QT interval. The paper speed is 25 mm/s, and the calibration is 10 mm = 1 mV.

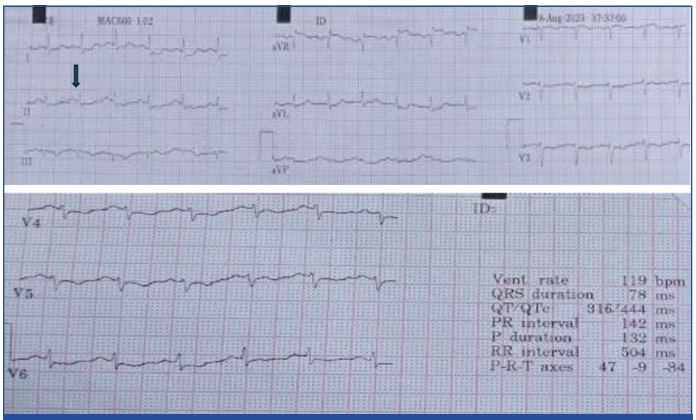
inversions with 1:1 atrioventricular conduction. Cardiac markers and serum potassium, calcium and magnesium were all within normal reference ranges. The patient was evaluated for other possible causes of new-onset bradycardia. The Two-Dimensional (2D) echo showed normal chamber dimensions, adequate Left Ventricular (LV) function with an ejection fraction of 65%. Cardiac markers measured serially were within normal limits. All the common possible causes of bradyarrhythmia were ruled out. No major drug-drug interactions are reported among chlorpheniramine, hydrocortisone, adrenaline, and fexofenadine, but caution is advised due to potential additive antihistamine effects between chlorpheniramine and fexofenadine and individual sensitivities [1,2]. Hence, a possibility of fexofenadine-induced bradycardia was suspected. At this point of suspicion, the patient had received three doses of 180 mg of oral fexofenadine at a 12-hour interval. Four hours post administration of the third and last dose of oral fexofenadine, further doses were withheld.

The following day, the patient developed palpitations and bradycardia with the lowest pulse rate recorded as 30 beats per minute. The patient was given a dose of intravenous injection of atropine 0.6



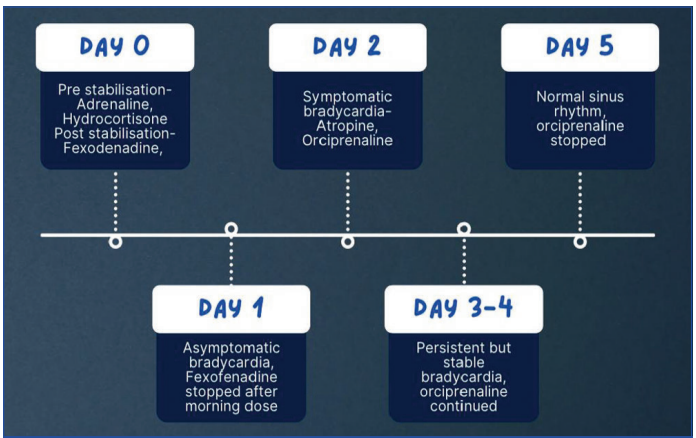
[Table/Fig-2]: Twelve-lead electrocardiogram taken after three doses of oral Fexofenadine showing marked sinus bradycardia indicated by the arrow. The heart rate measured was 42 beats per minute, with low voltage QRS complexes, PR and QTc intervals with no significant ST segment changes or T wave abnormalities. The paper speed is 25 mm/s, and the calibration is 10 mm=1 mV.

mg; following this, there was significant relief in her palpitations, and her heart rate transiently increased to 120/min, which settled shortly. [Table/Fig-3] shows the ECG taken post-injection of atropine administration.



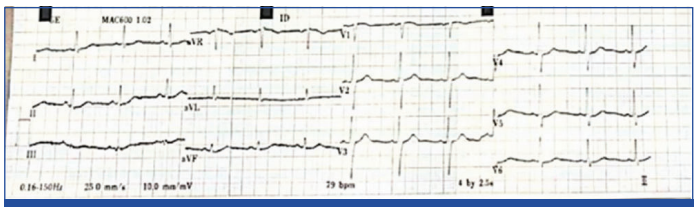
[Table/Fig-3]: Twelve-lead electrocardiogram taken post-injection of atropine administration, showing sinus tachycardia as marked by the arrow. The heart rate was 119 beats per minute, with narrow QRS complexes, PR and QTc intervals. The paper speed is 25 mm/s, and the calibration is 10 mm = 1 mV.

The patient was started on tablet Orciprenaline 10 mg thrice daily. The tilt table test was not done. The patient's heart rate did not show much improvement till day 4 post-Fexofenadine intake. On day 5 of admission, the patient's heart rate started improving to 75 beats per minute and orciprenaline was stopped. No further bradycardia was noted. The patient eventually recovered after 6 to 7 half-lives of the drug. This entire timeline of events is represented pictographically in [Table/Fig-4]. The patient was advised to undergo an allergy workup to identify the possible cause of anaphylaxis but refrained due to financial constraints.



[Table/Fig-4]: Diagrammatic representation of major events, initiation, duration and withdrawal of drug therapy.

The patient, on further follow-up after one week, had a heart rate of 82 beats per minute, and the ECG showed normal sinus rhythm with a ventricular rate of 79/min [Table/Fig-5]. Naranjo score was calculated to be 7, signifying that Fexofenadine is the most likely cause of the development of symptomatic sinus bradycardia in this patient.



[Table/Fig-5]: Twelve-lead electrocardiogram taken during review showing normal sinus rhythm, with heart rate approximately 90 beats per minute, narrow QRS complexes, PR and QTc intervals and no significant ST segment changes and T wave abnormalities. The paper speed is 25 mm/s, and the calibration is 10 mm = 1 mV.

DISCUSSION

Antihistamines alleviate allergic symptoms by blocking H1 receptors [3]. First-generation agents, though effective, caused undesirable cholinergic, dopaminergic, and serotonergic side effects, prompting the development of second- and third-generation drugs with improved safety profiles [4]. Cardiotoxicity, particularly QTc prolongation leading to torsades de pointes and cardiac arrest [5,6], has been a concern, resulting in the withdrawal of drugs like astemizole and terfenadine. Fexofenadine, terfenadine's active metabolite, remains widely used due to its cardiac safety, with animal studies showing no impact on cardiac ion channels [7,8]. However, rare cases of fexofenadine-induced bradyarrhythmia have been reported, though the mechanisms remain rather unknown [9]. In this patient, symptoms emerged after three doses of 180 mg oral fexofenadine, with other causes of bradycardia excluded. Serial ECGs showed no QTc prolongation calculated using Bazett's formula, and sinus rhythm was not restored despite atropine and orciprenaline administration. Fexofenadine's half-life ranges from 11 to 15 hours, with a mean of 14.4 hours for 60 mg doses [10]. To reduce plasma levels below the minimum effective concentration (15 ng/mL), 6-7 half-lives are needed [11]. This patient resumed sinus rhythm four days after the last dose, aligning with a calculated plasma concentration of 9.843 ng/mL, confirming drug-induced bradyarrhythmia. The effect was refractory to standard interventions, highlighting a rare adverse response to fexofenadine. However, the limitations of this include the inability to perform 24-hour Holter monitoring and serum drug levels assessment due to logistical reasons.

The other plausible causes of bradycardia were taken into consideration and evaluated in detail before correlating it to fexofenadine, the first one being anaphylaxis-related reflex bradycardia, as anaphylaxis itself can present with sinus/relative bradycardia and shock; one may consider that bradyarrhythmia may be disease-mediated rather than drug-caused [12]. Contrary to the previous statement, the ECG taken at the time of anaphylaxis showed a normal sinus rhythm despite shock at presentation. Among the other drug exposures, even though there are few case reports on epinephrine-induced reflex bradycardia or atrioventricular blocks [13-15], the profound and persistent bradycardia occurred many hours after administration of a single dose of intramuscular adrenaline in the emergency room. The kinetics do not fit in this case. There are no reports available to suggest that drugs such as cefixime, aceclofenac, and hydrocortisone, to which the patient has been exposed concurrently, are causing sinus bradycardia, thereby keeping fexofenadine as a potential cause. Intrinsic conduction system defects, including sinus node dysfunction and AV node disease, were highly unlikely.

Bradycardia appeared first, post administration of three doses of 180 mg of oral fexofenadine, reaching a nadir heart rate of 30 beats per minute and resolving gradually over the next four days. This

temporal course maps onto the pharmacokinetics of fexofenadine explained above. Other competing reversible causes like electrolyte imbalances, sepsis, structural cardiac diseases, myocarditis, acute coronary syndromes, and hypothyroidism were ruled out effectively. Fexofenadine has been linked temporally to high-degree AV blocks and bradysystolic arrest, according to a peer-reviewed case report that details a near-fatal bradyarrhythmic cardiac arrest that occurred within 36 hours of starting the medication, with no other cause found, clinical recovery following drug withdrawal without the need for a pacemaker, and no recurrence on follow-up [16]. A 6-week prospective cohort study of fexofenadine at 180 mg per day for management of chronic idiopathic urticaria reported no cardiac arrhythmias or QTc prolongation, along with clinical data insinuating that fexofenadine does not block the delayed rectifier potassium current [17]. Though fexofenadine does not block rapid potassium channels at therapeutic levels, the possibility of autonomic or Atrioventricular (AV) nodal effects can be considered as a plausible cause of sinus bradycardia without causing QTc prolongation. A Naranjo score of 7 [18], supported by a clear temporal relationship, exclusion of alternative etiologies, objective ECG evidence, and consistent published precedents, sums to probable causality, indicating fexofenadine being the most likely cause of sinus bradycardia in this patient.

CONCLUSION(S)

A relatively cardio-safe second-generation antihistamine, fexofenadine, that is commonly used for alleviating various allergic manifestations and anaphylaxis, has the potential to precipitate symptomatic bradyarrhythmia as explained in this case report, while the exact mechanism remains unknown. This case report uncovers possible adverse cardiac events and event-related deaths associated with fexofenadine, thereby necessitating caution while prescribing it. Though its action is subpar in the management of anaphylaxis, it is still recommended for treating allergic reactions.

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