

## CASE REPORT

## Fluphenazine decanoate-induced bradycardia: A case report

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**Abstract**

Sinus tachycardia and orthostatic hypotension have been so far reported among the negative cardiovascular complications of antipsychotic agents. This study aimed to report a case with bradycardia induced by fluphenazine decanoate administration. The patient was a 29-year-old man, admitted to the general teaching hospital in Sari, Iran, with a complaint of abdominal and gastric pain as well as weight loss following 7 months of fasting based on religious delusions. The patient developed bradycardia, 36 hours after fluphenazine decanoate administration. His pulse rate was also 46 beats per min (bpm). The antipsychotic medication was thus held and the patient did not take any drugs. On the 21st day after discontinuing this agent, the pulse rate reached 70bpm. This case report notifies that much more attention should be paid to all patients before starting fluphenazine decanoate administration, and close cardiac monitoring must be done.

**KEYWORDS**

antipsychotic agents, bradycardia, case report, fluphenazine decanoate

**1 | INTRODUCTION**

Antipsychotic agents are administered for the management of schizophrenia and schizoaffective disorders.<sup>1</sup> Long-acting injectable antipsychotics are usually prescribed for maintenance therapy in non-compliant/non-adherent psychotic patients.<sup>2</sup> The negative cardiovascular complications of antipsychotic agents include sinus tachycardia, orthostatic hypotension, polymorphic ventricular tachycardia (VT), for example, torsade de pointes or (TdP), myocarditis, cardiomyopathy, and myocardial infarction (MI).<sup>3,4</sup> A case report

in this field had accordingly revealed bradycardia and prolonged QTc interval upon using ziprasidone in a 25-year-old man.<sup>5</sup> Another case had further reported sinus bradycardia, chest pain, and syncope after 1.5 mg/day risperidone administration.<sup>6</sup> Moreover, symptomatic bradycardia and hypotension had been simultaneously detected while taking quetiapine in a 72-year-old individual with a history of heart disease.<sup>7</sup>

Fluphenazine decanoate, as a conventional or first-generation antipsychotic (FGA) agent, is a member of the phenothiazine-derived neuroleptics, which acts principally through the antagonism of

**Abbreviations:** ALP, Alkaline Phosphatase; BS, Blood Sugar; Cr, Creatinine; Hb, Hemoglobin; INR, International Normalized Ratio; K, Potassium; Na, Sodium; Plt, Platelet; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; RBC, Red Blood Cell.; SGOT, Serum Glutamic Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase; WBC, White Blood Cell.

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postsynaptic dopamine-2 receptors (D2Rs) in mesolimbic, nigrostriatal, and tuberoinfundibular pathways. This medication is accessible in various forms, namely, oral tablets and short acting, decanoate (depot) and enantoate ampules.<sup>8</sup> The effect of fluphenazine decanoate lasts for about 4–6 weeks.<sup>9</sup> Anticholinergic and extrapyramidal symptoms, such as sedation, dizziness, obesity, constipation, dry mouth and eyes, blurry vision, and urinary retention, are also among the common adverse reactions of fluphenazine decanoate.<sup>9,10</sup> The reported cardiovascular adverse effects of fluphenazine decanoate are myocarditis, cardiomyopathy, orthostatic hypotension with low incidence risk and corrected QT prolongation, and TdP with medium incidence risk.<sup>8,11,12</sup>

Since no case of fluphenazine decanoate-induced bradycardia has been so far documented; this report is about the patient who developed this complication.

## 2 | CASE PRESENTATION

The patient was a 29-year-old single man, holding a high-school diploma and residing in a village in northern Iran, with a history of schizophrenia. In the summer of 2018, he was admitted to the general teaching hospital in one of the northern cities, Sari, Iran, with a complaint of abdominal pain, nausea, hematemesis, non-biliary vomiting, weakness, lethargy, and weight loss after the seven consecutive months of fasting due to religious delusions. According to the Islamic religion, the fasting means being not permitted to eat and drink anything from sunrise to sunset for 1 month. He was thus hospitalized owing to losing weight 20 kgs followed by religious delusions and elevated level of lipase with reference to his laboratory test results, namely, amylase = 89 U/L, lipase = 7.2 U/L, albumin = 5.7 g/dL, SGOT = 10 U/L, and SGPT = 6 U/L. Other laboratory test results also included WBC = 10.2, RBC = 4.76, Hb = 13.9 mg/

dL, PLT = 260, Cr = 1.1 mg/dL, Na = 139 mEq/L, K = 3.8 mEq/L, BS = 141 mg/dL, ALP = 124 IU/L, PT = 13 seconds, PTT = 25 seconds, and INR = 1.1. Given the religious and persecutory delusions and prolonged fasting, psychiatric consultation was thus requested.

After three-day hospitalization, the lipase marker decreased and the gastrointestinal symptoms recovered. Likewise, abdominal (viz. liver, gallbladder, and pancreas) sonography and electrocardiography (ECG) were normal (Figure 1). Therefore, the patient discharged from the gastroenterology ward and transferred to the consultation-liaison psychiatry unit at the same hospital.

He had psychotic symptoms since 2010. The latest date of admission to the psychiatry ward was 2016 with the presentations of sadness, impatience, social isolation, death wish, as well as persecutory and grandiose delusions and auditory hallucinations. Despite two times of hospitalization in the psychiatric ward at a psychiatric hospital, he had always discontinued oral antipsychotic medication on his own. During the last hospitalization, the patient discharged with risperidone 4 mg twice a day, olanzapine 5 mg at night, intramuscular (IM) flupenthixol decanoate weekly, and trihexyphenidyl 2 mg twice a day due to his non-response to a single drug. He continued IM flupenthixol decanoate for several months without any side effects, and then discontinued all the medications. As flupenthixol decanoate was not accessible at that time, it was replaced with fluphenazine decanoate. Therefore, 25 mg IM weekly injections of fluphenazine decanoate resumed for him during the recent hospitalization, after the prescription of oral fluphenazine 2.5 mg twice a day for 3 days. The patient, with no history of cardiovascular disease (CVD), became bradycardia and complained about lightheadedness and headache, 36 hours after fluphenazine decanoate administration. The pulse rate was 46 beats per min (bpm) and blood pressure was 70/50 mmHg. In addition to obtaining the sequential ECG and requesting the cardiology consultation, 500 cc normal saline was prescribed and the vital

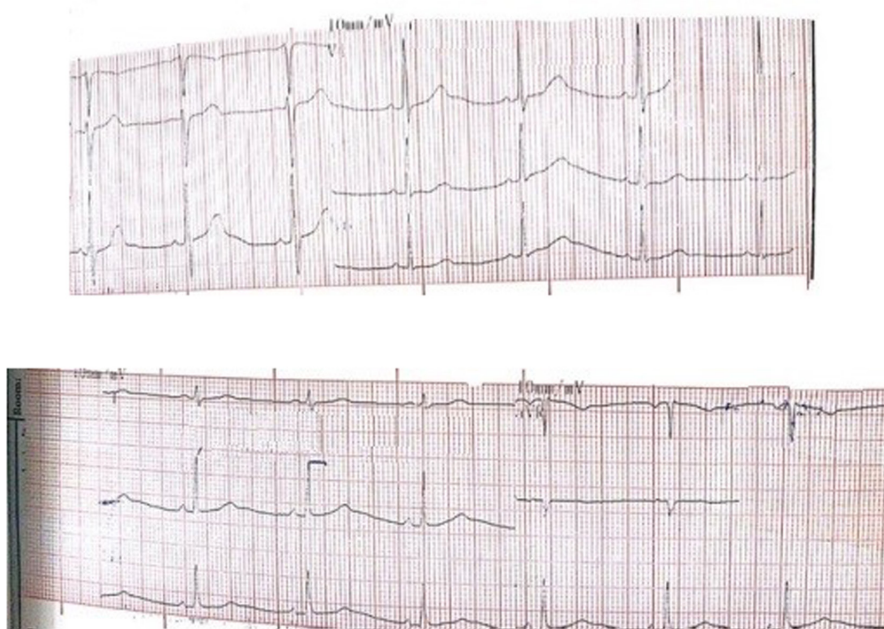


FIGURE 1 Patient's ECG, September 20, 2018-01 (Admission ECG)



signs were frequently and carefully checked (Figures 2–4). The antipsychotic medication was also held and the patient did not take any other antipsychotic drugs. On the 21st day after discontinuing fluphenazine decanoate, the heart rate reached 60 bpm (Figure 5) and that was 70 bpm in the last follow-up. The change trends in heart rate and blood pressure are shown in Charts 1 and 2, respectively. Given the severity of persecutory delusions 10 days after the heart rate returned to normal and considering the cardiology and anesthesiology consultation, electroconvulsive therapy (ECT) was given three times a week for eight sessions in total. After the ECT, 5 mg aripiprazole was prescribed, which reached 10 mg a day,



FIGURE 2 Patient's ECG, September 26, 2018 (ECG after the administer the fluphenazine decanoate)

and the patient discharged with aripiprazole (10 mg/daily), biperiden (2 mg twice a day), vitamin D<sub>3</sub> (50,000 unit once a week), and vitamin B<sub>1</sub> (100 mg daily).

### 3 | DISCUSSION

In this study, the patient showed bradycardia induced by fluphenazine decanoate. His dramatic change in the pulse rate also noted some complications, and fluphenazine decanoate with a probably score of 9 according to the Naranjo Adverse Drug Reactions (ADR) probability scale was considered as the reason behind bradycardia in this patient (Table 1).<sup>13</sup> Bradycardia has been so far reported following the use of non-antipsychotic and psychotropic medications.<sup>14,15</sup> Cardiac and orthostatic side effects of fluphenazine decanoate may thus reveal due to the action of this medication as an antagonism of alpha-1 ( $\alpha_1$ ) adrenergic receptors.<sup>16,17</sup>

In this line, Calderone et al. had reported the alternations of cardiac repolarization, where in TdP might be seen after starting FGAs, including fluphenazine decanoate,<sup>18</sup> but a Swedish nationwide study had classified this agent as a non-TdP labeling antipsychotics.<sup>19</sup> Burton et al. had further reported a 61-year-old man with schizophrenia admitted to an emergency department with the chief complaint of chest pain and shortness of breath. The first fluphenazine decanoate injection had been administered approximately 2 weeks prior to presentation, and the second IM injection had been due on the day the patient had presented to the hospital. T-wave abnormality and atrial fibrillation with aberrant conduction or ventricular premature complexes had been also detected on the ECG after fluphenazine decanoate administration.<sup>20</sup> The main inconsistency was the history of coronary artery disease and atrial fibrillation that did not exist in the present case. Previously, the first-degree atrioventricular (AV) block had been seen in three cases undergoing treatment with olanzapine,<sup>21,22</sup> which had decelerated AV conduction with an unknown mechanism as an antipsychotic medication. The similarity of these cases with the present one was the clinical manifestations, such

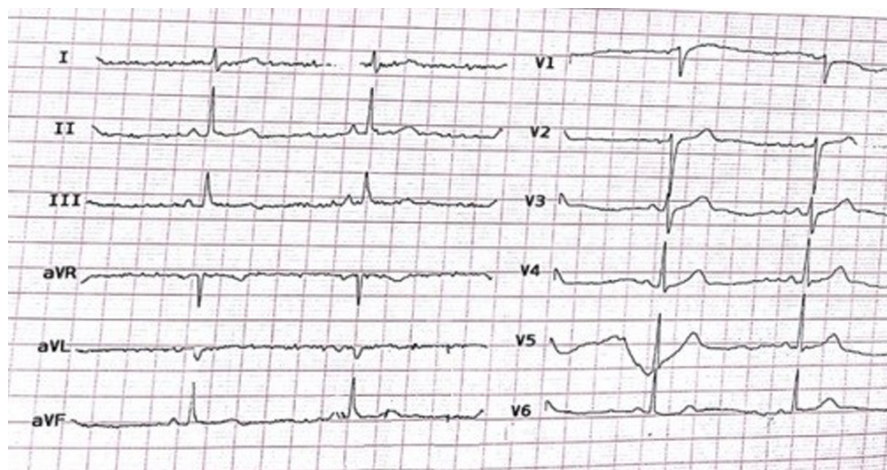


FIGURE 3 Patient's ECG, September 29, 2018



FIGURE 4 Patient's ECG, October 3, 2018

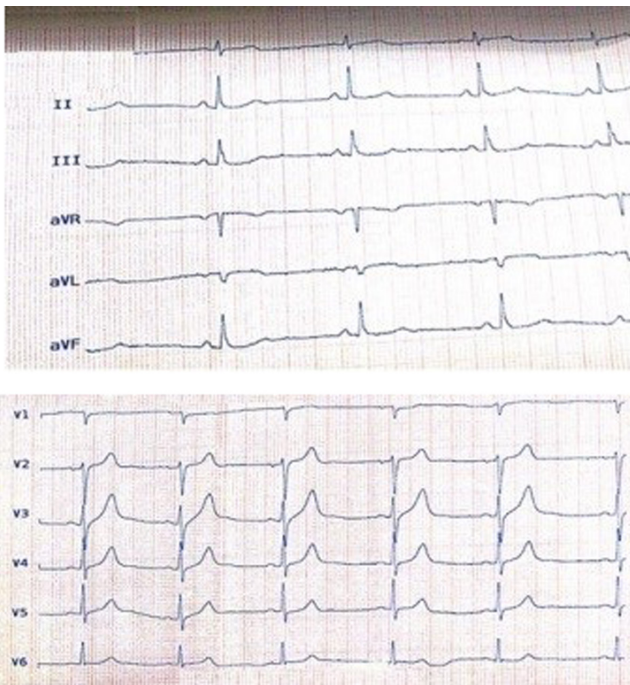
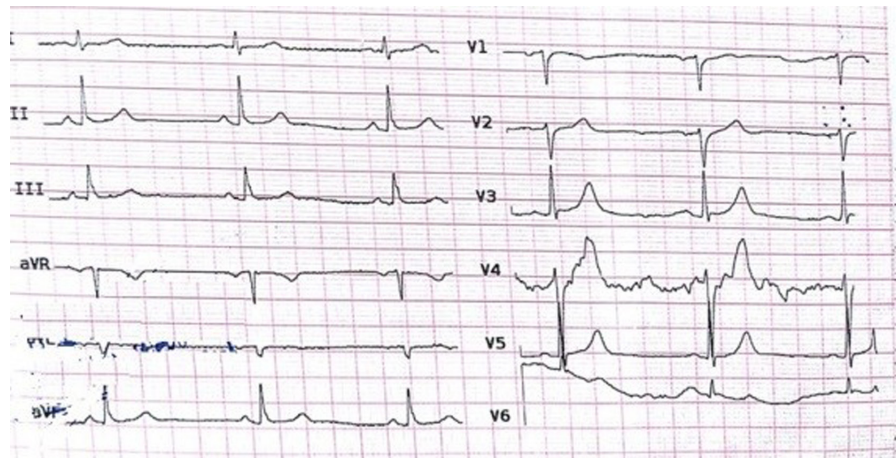


FIGURE 5 Patient's ECG, October 13, 2018

as lightheadedness and reduced symptoms after interruptions in medication administration.

Besides, junctional bradycardia had been observed in a 65-year-old patient with bipolar affective disorder who had initiated quetiapine for manic episodes. Physical examinations had also revealed the regular pulse rate of 50 bpm and decreased blood pressure (90/60 mmHg). This clinical manifestation had disappeared 4 days after discontinuation of the medication.<sup>23</sup> Another case, who had committed suicide with thioridazine, had similarly revealed persistent third-degree AV block, progressive hypotension, and TdP episode that had disappeared within 48 hours after stopping the drug.<sup>24</sup> Bradycardia had been seen under the overdose condition in that case, but this slower-than-normal heart rate was detected in therapeutic dose in the present

case. Moreover, 45 minutes after the IM injection of ziprasidone in a 70-year-old female patient due to persecutory delusions and auditory hallucinations, she had lost her consciousness, and the ECG had shown third-degree AV block with 30–40 bpm; so that the medical team had started cardiopulmonary resuscitation (CPR).<sup>25</sup> Furthermore, Olgun et al. had reported an 8-year-old boy admitted to a hospital with the chief complaint of syncope according to the administered risperidone 2 weeks later due to his agitation and sleep disorder. Close monitoring had accordingly revealed sinus bradycardia with episodes of sinus arrest.<sup>26</sup> It had been also suggested that risperidone could act as the class-III antiarrhythmics and cause bradycardia. In addition, another 12-year-old boy had presented one episode of chest pain, lasting 1 hour within 1 month after olanzapine administration. The first-degree AV block had been also depicted in the ECG. Rajput et al. believed that such a medication could slow down the phase-four depolarization and then decrease sinus node automaticity.<sup>22</sup> All these case reports demonstrated the probability of bradycardia following the onset of some antipsychotics, both FGAs and atypical antipsychotics that may develop in any age regardless of the underlying cardiovascular disease.

The baseline ECG should be thus done in all patients, especially those with a history of cardiac conduction abnormalities before fluphenazine decanoate administration, and then cardiac monitoring must be considered. Besides, symptoms such as dizziness or lightheadedness after fluphenazine decanoate injection should be taken seriously and close examinations should be performed.

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#### CONFLICT OF INTERESTS

The authors declare that they had no conflict of interests.

#### AUTHORS' CONTRIBUTIONS

Mahsa Kamali contributed to the writing the primary manuscript, describing the case, and editing of the manuscript. Forouzan Elyasi performed the primary and psychiatric evaluation of the case,



patient heart rate

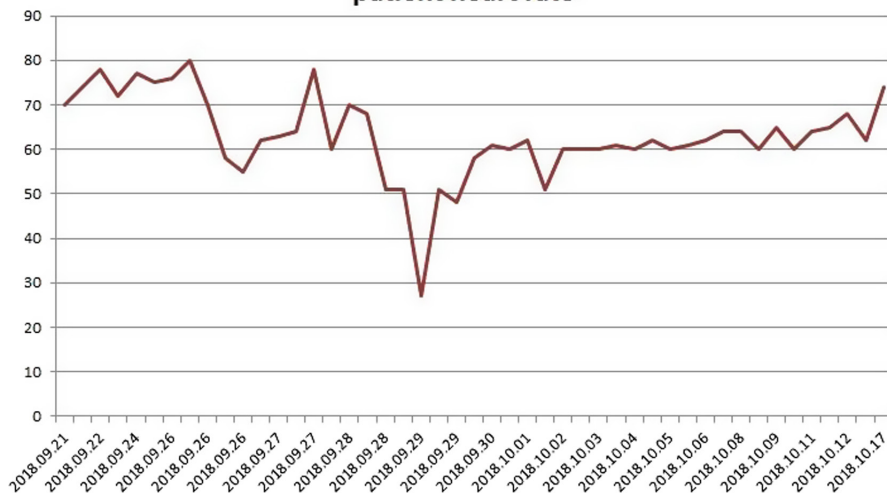


CHART 1 Trend change in patient's heart rate

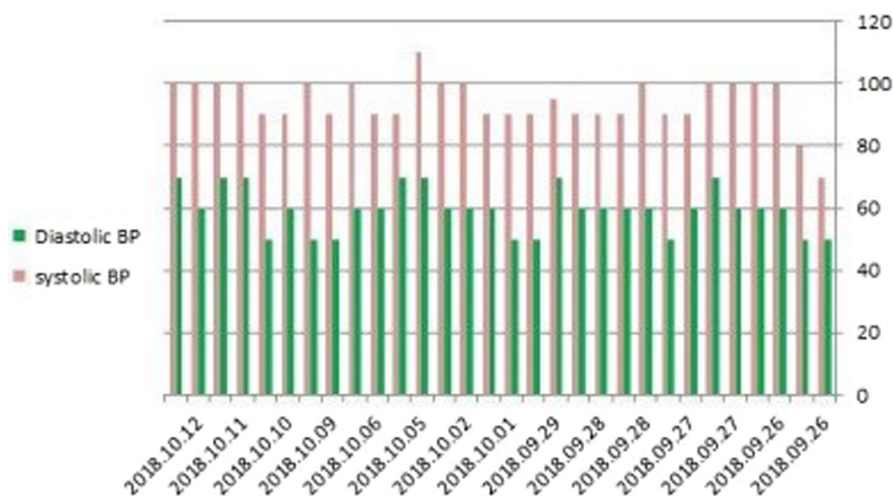


CHART 2 Trend change in patient's blood pressure

TABLE 1 Naranjo adverse drug reaction probability scale: To assess the adverse drug reaction

Options	Yes	No	Do not know	Score
1. Are there previous conclusive reports of this reaction?	*			+1
2. Did the adverse event appear after the drug was given?	*			+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	*			+1
4. Did the adverse reaction reappear upon readministering the drug?			*	0
5. Were there other possible causes for the reaction?		*		+2
6. Did the adverse reaction reappear upon administration of placebo?		*		+1
7. Was the drug detected in the blood or other fluids in toxic concentrations?			*	0
8. Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	*			+1
9. Did the patient have a similar reaction to the drug or a related agent in the past?		*		0
10. Was the adverse event confirmed by any other objective evidence?	*			+1
Total score: 9				

management of case, contributed in the conception of the work, describing the case, and editing of the manuscript. **Mehran Zarghami** was previous psychiatrist of patient and contributed to scientific

editing and language editing of the manuscript. **Marzieh Azizi** contributed to the writing the primary manuscript. All authors read and approved the final manuscript.

## INFORMED CONSENT

Written informed consent was obtained from the patient for the publication of this report.

## DATA AVAILABILITY STATEMENT

All data provided during this study are included in this article. The data are not publicly available due to privacy restrictions. Further enquiries can be directed to the corresponding author.

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