Case report

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A case of hypotension and heart rate changes on rechallenge with a low dose of clozapine with no apparent secondary cause

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Abstract

Clozapine is known to cause innocuous as well as severe and or fatal cardiovascular side effects. These side effects are commonly reported at the initiation of clozapine therapy. We report a patient who was stable on clozapine for several years but in whom we had to withhold clozapine for medical reasons and subsequently developed significant hypotension and heart rate changes when rechallenged with a small dose of clozapine.

Key words: clozapine, side effects, cardiac, heart rate, hypotension

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Introduction

Clozapine is considered the gold standard medication for resistant schizophrenia but is also associated with several cardiometabolic side effects such as orthostatic hypotension, tachycardia, myocarditis, cardiomyopathy, dyslipidaemia, weight gain and obesity (1, 2).

We present a patient with a stable mental state while on 100 mg a day of clozapine for the last three years, who presented with exertional dyspnoea and tachycardia which resulted in clozapine being withheld and who subsequently developed a significant postural drop in blood pressure and bradycardia on rechallenge with a small dose of clozapine.

Case report

Miss X was a 23-year-old single, unemployed female living with her parents. She was diagnosed with schizophrenia at the age of 17 years and had been started on clozapine at the age of 19 years, due to resistance to several antipsychotics (including an atypical antipsychotic) despite being treated with therapeutic doses and good compliance. Prior to this presentation, her blood pressure and pulse rate were in the normal range. However, her body mass index was 30.5 kg/m^2. Her electrocardiogram (ECG) and echocardiogram were normal. In addition, all her haematological and biochemical tests including fasting blood sugar, lipid profile and thyroid function tests were in the normal range. There was no past or family history of cardiac events.

She presented to the outpatient department in January 2022, complaining of shortness of breath on exertion and palpitations of four days duration prior to the presentation. On admission, her blood pressure was 120/70 mmHg and her pulse rate was 130 beats per minute (bpm). Her temperature was normal. She did not complain of chest pain and did not have symptoms suggestive of depression, panic attacks, or other anxiety disorders. She did not have any psychotic symptoms (including delusions of control, nihilistic or hypochondriacal delusions or somatic hallucinations) either. Her clozapine was stopped, and she was admitted to a medical ward to exclude any cardiac or pulmonary events as well as any infections or inflammatory conditions which could have given rise to the current presentation. All her investigations including the ECG, echocardiogram and troponin I levels were normal. She was negative for inflammatory markers and dengue antibodies. The polymerase chain reaction (PCR) for COVID-19 was negative.

After obtaining the cardiology opinion, we decided to rechallenge her with clozapine due to her previous excellent response to the medication. Her blood pressure and pulse rate prior to being rechallenged with clozapine were 120/80 mmHg and 72 bpm respectively.

After the first dose of clozapine of 12.5 mg, the patient complained of severe dizziness. Her blood pressure dropped to 70/40 mmHg and her pulse rate was 114 bpm. These parameters remained around the same values during the next eight hours. Her temperature was normal. Clozapine was withheld after discussing with the consultant cardiologist due to changes in the cardiac parameters. The patient was transferred to a medical ward for further monitoring. On the second day of the medical admission, her platelet count dropped from 227,000 to 156,000. However, the next day (the third day after developing the dizziness) it increased to 335,000. Dengue fever was suspected, but her temperature, full blood count, C reactive protein levels (CRP) were normal, and the dengue antibody test was negative. Her blood pressure and pulse rate returned to the regular values on the second day (48 hours after the initial drop). Her ECG, troponin levels and echocardiogram findings were normal. Her dizziness improved on the fourth day. At this point, she was not on any medication (psychotropic or otherwise).

She was again challenged with clozapine 12.5 mg one week after the first rechallenge. However, her pulse and blood pressure dropped again to 40 bpm and 70/50 mmHg respectively. A sinus arrhythmia was noted in her ECG (Figure 1). The echocardiogram was normal.

Figure 1. Cardiac monitor showing bradycardia and hypotension on rechallenging with clozapine.

We obtained a second opinion from another consultant psychiatrist and a cardiology opinion regarding her psychotropics and decided not to rechallenge with clozapine due to the significant fluctuations in cardiovascular parameters despite being administered a very small dose of clozapine.

Fourteen days after the admission the patient developed symptoms of a relapse of schizophrenia characterised by irritability and persecutory delusions. She was started on quetiapine and the dose was gradually built up to 800 mg. As she was still symptomatic, we added amisulpride and its dose was increased to 200 mg daily.

Currently, she is experiencing some residual psychotic symptoms, however, she is not distressed by them and is having a reasonable functional level.

Discussion

This patient who was stable on clozapine for three years developed sudden onset shortness of breath and tachycardia. No underlying cause for the exertional dyspnoea could be found. Several attempts to recommence clozapine resulted in a significant reduction in her blood pressure and heart rate fluctuations which led to the decision to stop clozapine.

Patients with severe mental illness are at risk of developing cardiovascular diseases due to their lifestyle (smoking, poor dietary habits, sedentary lifestyle) and antipsychotic related issues (3). Clozapine, olanzapine, and quetiapine are associated with an increased risk of weight gain, impaired glucose tolerance, dyslipidaemia and cardiovascular diseases (3). However, our patient did not have any of the above comorbidities apart from a BMI above 30 kg/m^2.

Clozapine has a high-affinity for adrenergic (α_1, α_2), dopamine (D_1, D_2 and D_4), serotonin (5-HT_{2A} and 5-HT_{2C} among others), muscarinic (M_1) and histaminergic receptors (H_1) which account for some of its cardio-metabolic side effects (2).

Previous reports suggest that around 9% of patients on clozapine develop orthostatic hypotension mainly due to the anticholinergic and α_1 blockade, and 6% of them go on to develop cardiogenic syncope (4). In addition, there are reports of dose-related QT prolongation among patients on clozapine (1). Myocarditis is a potentially fatal cardiac complication associated with clozapine and has been reported in about 3% of patients on clozapine (5). Most of the above cardiac events have been reported to occur within the first six weeks of starting clozapine (6).

Clozapine induced cardiomyopathy is generally reported to occur at a median time period of nine months after starting clozapine, however, there are reports of it occurring at other times in the course of treatment with clozapine (1,7). The mean dose of clozapine associated with cardiomyopathy is reported to be around 360 mg which is much higher than the dose our patient was on (4). Shortness of breath has been reported as the commonest clinical presentation (60%) in clozapine induced cardiomyopathy, followed by palpitations (36%) (4). Our patient presented with these symptoms initially; however, all her investigations were normal.

Tachycardia occurs in about 25% of patients on clozapine, with a mean increase of the heart rate of 10 to 15 bpm (8). It is postulated that the anticholinergic effects of clozapine causing vagal inhibition induce tachycardia.

Bradycardia has been reported as a cardiac side effect of clozapine. However, published reports on bradycardia in the absence of a secondary cause are limited (9). Our patient presented with tachycardia and later developed bradycardia in response to the clozapine treatment.

Clozapine induced severe cardiac side effects on the first dose or while on very low doses are rare and cardiac side effects of clozapine have been generally reported when the daily dose is around 100 mg (5).

The previous clinical records of this patient did not indicate any cardiac side effects when she was started on clozapine initially or during the three years she was on the medication. However, she developed cardiovascular symptoms within minutes after being rechallenged.

Our attempts to rechallenge with clozapine were not successful due to significant changes in the cardiac parameters. The cardiologist recommended considering administering a small dose of clozapine while increasing her fluid intake with added salts, fludrocortisone and a sympathomimetic if we did not have an alternative antipsychotic. However, considering the lack of resources to monitor and the practical issues of continuing such a regime, especially during the height of the COVID-19 outbreak, we opted to manage the relapse of psychotic symptoms with alternative antipsychotics despite her being resistant to several (olanzapine and risperidone) in the past.

Conclusions

No clear guidelines or consensus are available to manage patients who develop side effects with small doses of clozapine in the titration period. Even though our patient was not found to have myocarditis and or cardiomyopathy, these conditions were still possible with the continuation of clozapine titration and an early decision was required regarding continuation of clozapine. Further evaluation and research are needed in this area.

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Statement of contribution

MLH conducted the literature survey. All authors contributed to writing the manuscript and approved the final draft.

Conflicts of interest

None declared.

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