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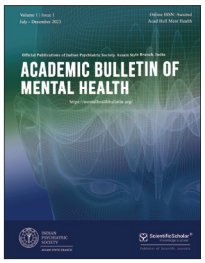

Case Report

Clozapine-induced Hypertensive & Tachycardia Twirls in a Schizophrenia Patient

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ABSTRACT

The effectiveness of clozapine, a second-generation antipsychotic, in treating schizophrenia that is resistant to treatment is well established. Rare adverse effects like tachycardia and hypertension, however, might also result from it. In this case study, a 30-year-old woman with schizophrenia experienced tachycardia and chronic hypertension following clozapine medication. The patient's heart rate and blood pressure were continuously raised, even though routine blood tests were within normal ranges. Eventually, atenolol was introduced to control these adverse effects. Although the precise mechanism by which clozapine causes tachycardia and hypertension is yet unknown, it is thought to be related to its alpha-adrenergic blocking capabilities and possible interactions with the D4 receptor. This case emphasises how crucial it is to start clozapine therapy with patients under strict observation for these unusual adverse effects

Keywords: Adverse Drug Reaction, Clozapine, Hypertension, Schizophrenia, Tachycardia

INTRODUCTION

Clozapine is a second-generation, atypical antipsychotic mainly prescribed for schizophrenia that is resistant to other treatments.[1] Clozapine has special receptor-binding abilities, like high dopamine dopamine receptor (D2/D4) affinity and significant histaminergic, muscarinic, and alpha-adrenergic blocking properties that make it different from other antipsychotic drugs. Besides its efficacy, this drug also causes different side effects.[2] While seizures, postural hypotension, constipation, and neutropenia are commonly reported, instances of new-onset persistent hypertension & tachycardia are rare.[3] In this case report, we present a case of a 30-year-old female who developed hypertension.

CASE REPORT

This patient was a 30-year-old Hindu, unmarried woman, higher secondary pass, hailing from an urban locality, joint family, and middle socioeconomic background, suffering from schizophrenia for more than 7-8 years with no family history of any psychiatric illness, chronic illnesses, or comorbidities (like hypertension, type 2 diabetes mellitus, etc.). The patient suffered from persecutory delusions, auditory hallucinations, negative symptoms, self-muttering, running away from home, wandering aimlessly on roads, poor self-care, and grossly declined socio-occupational functions.

The patient underwent regular treatment with various trials of both first- and second-generation antipsychotic drugs (e.g.- Olanzapine, quetiapine, risperidone, haloperidol) with adequate dosage

for the last 6 years and no substantial improvement. This patient also received multiple electroconvulsive therapies (given a few years prior) but showed poor response.

At the time of the first presentation in February 2024, she was on an adequate dose of Olanzapine, Quetiapine, and Risperidone for the last 2 months, but no further improvement was noticed. Hence, the patient was diagnosed with treatment-resistant schizophrenia. Admission and further treatment with clozapine initiation and tapering of previously administered antipsychotics were planned.

On the day of admission (day 1), physical examination was non-significant, and vitals and hemodynamics were stable. Her weight was 81 kg, body mass index was 23.6 kg/m^2, Pulse rate (PR) was 72 bpm, blood pressure (BP) was 110/70 millimetre of mercury (mm Hg), respiratory rate was 18/min, and peripheral capillary oxygen saturation was 97% at room air. The routine blood investigations [Complete Blood Count, Random Blood Sugar, liver & kidney function tests, serum thyroid-stimulating hormone (TSH)] showed no abnormalities and electrocardiogram showed sinus rhythm.

According to the treatment plan, a pre-clozapine evaluation was done, and the clozapine dosage was augmented to 12.5 mg twice per day on day 4 with a baseline BP of 110/72 mm Hg before the day of initiation of clozapine. According to the treatment plan, the dose was increased by 25 mg on the 3rd day until the 300 mg/day target dose was achieved, accompanied by slow tapering of the previous antipsychotics.

Soon after starting on clozapine, the patient's BP (more than 160/100 mm Hg) and heart rate (HR) (more than 110 bpm) elevated persistently as recorded on a daily basis at a 50 mg/day (day 7th-9th) and 75 mg/day (day 10th-12th) dose. The BP of the patient was monitored every 6 to 8 hours and an increase in both systolic and diastolic BP was noticed from day 7th to day 12th of admission. In addition, tachycardia was also observed during those days at the 50 mg/day (day 7th-9th) and 75 mg/day (day 10th-12th) clozapine dose. During the whole period after clozapine initiation, routine blood investigations, particularly complete hemogram, liver & kidney function tests, serum electrolytes, fasting blood sugar, serum TSH, etc. were repeated and remained within normal values. Besides clozapine, additional medication included tablet Pantoprazole 40 mg per day. BP showed maximal recorded systolic blood pressure (SBP) at 150 to 170 mm Hg and diastolic blood pressure (DBP) at 100-120 mm Hg with a HR more than 110 bpm. Tablet Atenolol 25 mg/day was finally added on the day of 12th of admission and patient's BP improved. After administration of tablet Atenolol 25 mg/day, the maximal daily BP now remained between 110 to 130 mm Hg of SBP & 74 to 88 mm Hg of DBP from day 12th to day 15th of admission. The tablet Atenolol 25mg/day was stopped for the next 3 days (day 16th-18th). BP recording showed an SBP more than 150 mm Hg and DBP more than 100 mm Hg and HR more than 100 bpm. Thus, rechallenging with clozapine was done twice resulting in a similar hypertensive and tachycardic response at the same dosage (50 mg/day & 75 mg/day), which was again managed by the clozapine and in combination with tablet atenolol 25 mg/day and planned to monitor BP and HR investigation reports and vitals of the patient during the stay in the hospital are tabulated and is shown in Table 1.

DISCUSSION

Clozapine is a second-generation atypical antipsychotic mainly prescribed for schizophrenia that is resistant to other treatments. It is rarely associated with hypertension. Clozapine is a potent α-adrenoreceptor blocker (α-2 > α-1).[2] So, the paradoxical rise in noradrenergic plasma levels can cause hypertension & tachycardia. Another probable explanation, is the inhibition of the D4 receptor, because germline deletion of D4 receptor in mice causes hypertension.[4] This germline deletion of D4 receptor may cause increased renal expression of the angiotensin type 1 receptor (AT_1R) and renal expression of sodium exchangers, transporters, and pumps, e.g., NHE3(Sodium-Hydrogen Exchanger 3), NKCC2 (Na^+-K^+-$2Cl^-$ cotransporter 2), NCC (Sodium-Chloride Cotransporter), and Na^+ - K^+/ATPase, α subunit. In mice, clozapine administrated subcutaneously (20 mg/kg/day x 3 days, n=5), causes induced hypertension, shifts the pressure-natriuresis plot to the right, and increases the renal expression of NCC (Sodium-Chloride Cotransporter) and Na^+K^+/ATPase, α subunit, relative to vehicle-treated mice (n=5). Activation of D_4R causes decreased AT_1R expression and Na^+ - K^+/ATPase activity in rat renal proximal tubule cells (RPTCs).[2,4]

A few cases have been reported regarding hypertension. When hypertension occurs, then hypotensive treatment is necessary. Tachycardia may occur in the early stages of treatment but is usually benign in nature; it may be dose related. When tachycardia is persistent even at rest, it may be associated with fever, hypotension, or chest pain that may be indicative of myocarditis. Then, referral to the cardiologist is advised with concluding the dosage of clozapine. This case hereby emphasizes the importance of considering this atypical presentation of hypertension and tachycardia as clozapine-induced side effects, which may or may not be dose-related.

The exact etiology of clozapine-induced tachycardia and hypertension is still unknown. Several risk factors may be associated with it. Rapid increases in clozapine dosage may be one of the causes. But no evidence has yet been presented. Usually, it is reported that clozapine-induced hypertension and tachycardia present in the first 4 weeks but sometimes persist longer. Pre-existing medical conditions in the patient may

Table 1: showing investigations and vital parameters of the patient over time

Investigations/ Vitals (after diagnosing)	Day 1	Day 7	Day 10	Day 14	Day 17	Day 25
Haemoglobin (gm%)	11	10.2	-	9.1	-	10.9
RBC (mil/mcl)	3.95	3.02	-	3.46	-	4.00
Leukocyte (/mcl)	8790	7850	-	6880	-	9500
Neutrophil	80	78	-	74	-	83
Lymphocyte	16	16	-	10	-	12
Platelets (/ mcl)	1.40 X 100000	1.74 X 100000	-	1.62 X 100000	-	1.68 X 100000
ESR (mm/hour)	36	59	-	50	-	32
Serum creatinine (mg/dl)	0.80	0.60	-	0.52	-	0.44
Serum TSH (μU/mL)	-	1.3	-	1.2	-	-
Serum Na (mEq/L)	-	141.6	140.5	142.80	137.2	139
Serum K (mEq/L)	-	3.4	4.2	3.2	2.9	3.1
Serum CPK (mcg/L)	-	260	-	180	-	105
Body temperature (F)	98.2	97.6	98.1	98	-	97.5
BP (mm of Hg)	110/70	160/100	170/110	128/90	150/110	130/80
Heart rate (beats per minute)	72	120	146	90	134	88
RR (beats per min)	18	20	16	20	18	20
SpO_2 (%)	97% (with room air)	98% (with 2-4 Lt O_2)	99% (with 2-4 Lt O_2)	97% (at room Air)	96% (at room air)	98 % (at room Air)

RBC: Red blood cell, ESR: Erythrocyte sedimentation rate, TSH: Thyroid-stimulating hormone, Na: Sodium, K: Potassium, CPK: Creatine Phosphokinase BP: Blood Pressure, mm of Hg: Millimeter of mercury, RR: Respiratory Rate, SpO_2: Peripheral capillary oxygen saturation.

also precipitate these side effects. Sometimes, use of clozapine over a prolonged period causes weight gain that may lead to hypertension. Few evidence suggests a potential role of genetic susceptibility, i.e., the germline deletion of D4 receptors. Clozapine-induced hypertension often occurs in the initial treatment phase (62.5 to 250 mg/day) are predominantly reported in males aged 32-49.[5-8] In 1988, Kane *et al.* in this study it is observed that hypertension in 12% of patients was managed with clozapine, which was higher than 5% reported among patients receiving chlorpromazine.[9] Deepak *et al.*, in 2021, in a case report, mentioned that clozapine may cause persistently high BP in association with severe loss of cardiac autonomic tone and parasympathetic activity accompanied by normal sympathetic activity.[10] In 2017, Grover *et al.*, in a case report, mentioned that a 32-year-old male developed hypertension during clozapine treatment initiation.[11]

The question of whether any specific clozapine dose triggers hypertension and tachycardia is still fascinating, yet difficult to answer due to very much lack of journals on this topic. A study showed increased BP after 3 months of treatment of clozapine.[12] Besides, a case report mentioned about a 32-years-old male developed hypertension during clozapine treatment initiation.[11] Some factors also need to be considered like the following. Individual variability: Patients may have differing susceptibilities to hypertension and tachycardia at varying dose levels. Confounding factors: Pre existing conditions, any comorbidity or concomitant medications might play a role in increasing BP and HR, even at seemingly low clozapine doses. Limited generalizability: Only a few case reports are available that represent unique clinical scenarios but do not show the broader population trends.[13,14] Therefore, the available evidence suggests a possible dose-dependent association, still, more studies or literature are significantly needed to establish a definitive relation.

CONCLUSION

Prompt diagnosis and intervention are crucial for successful management of clozapine-induced hypertension and tachycardia. Key strategies include the withdrawal of clozapine immediately or by tapering. Managing vitals, electrolyte imbalances, and hydration is essential. Also advised for correcting anemia, edema, other symptoms, or comorbidities. Referral to the cardiologist is advised. Also, Clozapine should be held if increased HR occurs as a cardiorespiratory issue. Benign sinus tachycardia may be treated with bisoprolol or atenolol, though the previous

literature is not supportive. This case reinforces/underlines the potential for clozapine to prompt hypertension requiring pharmacological intervention, foregrounding the need for careful monitoring and management of B.P. & H.R. levels in the patients who are undergoing treatment with this antipsychotic drug (clozapine).

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