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Case Report

Rapid-onset supraventricular tachycardia following clozapine initiation and its management with verapamil: a case report

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ABSTRACT

Clozapine is the drug of choice for treatment-resistant schizophrenia. However, the use of clozapine is limited by its serious adverse effects, which often underlie its discontinuation. The cardiovascular side effects that raise safety concerns include tachycardia, myocarditis and cardiomyopathy. The development of clozapine-induced tachycardia is usually observed on higher dosage especially at early stages of treatment. Here, author presented the case of a patient with treatment-resistant schizophrenia who developed asymptotic supraventricular tachycardia despite low dose of clozapine at the second day of treatment. Additionally, author explored the possibility of clozapine re-challenge in combination with verapamil treatment.

Keywords: Arrhythmia, Clozapine, Psychosis, Supraventricular tachycardia, Schizophrenia, Verapamil

INTRODUCTION

Schizophrenia is a chronic, debilitating mental illness that affects approximately 1% of the population. While most patients respond to one or two trials of antipsychotic treatment, 20-30% remain resistant to this pharmacological approach.[1]

Clozapine, an atypical antipsychotic from the dibenzothiazepine family, is the treatment of choice in such cases.[2,3] It is also used to treat resistant mania and reduce suicide risk and aggressive behavior.[4]

While the effects of clozapine are well established in the literature, potentially serious adverse effects limit its use as a third-line antipsychotic.[2-5] Cardiac-related events are the most concerning, yet uncommon, side effects of clozapine. These include tachycardia, myocarditis, cardiomyopathy, blood pressure fluctuations, syncopal attacks and electrocardiogram (ECG) abnormalities.[5] Clozapine-induced sinus tachycardia occurs in approximately 25% of patients with a mean increment of 10 to 15 beats per minute (bpm) due to the anticholinergic properties of clozapine.[5,6]

Supraventricular tachycardia (SVT) which less commonly observed with clozapine use, differ from sinus tachycardia in which the rate in sinus tachycardia is 100-150 bpm while the rate in SVT is 151-250 bpm. In addition, the P waves and T waves are separated in sinus tachycardia while they are together in SVT.[7]

Here, authors have reported the case of a 29-year-old female with treatment-resistant schizophrenia who developed asymptotic supraventricular tachycardia (SVT) on the second day of clozapine initiation, which was then successfully managed through the addition of verapamil to the treatment regimen.

CASE REPORT

In August 2016, a 29-year-old physically healthy, non-smoking female with schizophrenia was admitted to the psychiatric unit of general hospital in Riyadh, Saudi Arabia for the first time. This patient presented with acute exacerbation of schizophrenia-related symptoms in the form of delusions of persecution and auditory hallucinations in addition to prominent depressive symptoms, likely resulting from poor adherence to her medications. Since, her diagnosis five years prior, she maintained stability using olanzapine (15 mg/day) and fluvoxamine (200 mg/day) and regular supportive psychotherapy sessions that helped her to accept her illness and cope with the residual symptoms. After a thorough assessment, her previous medications were resumed with the dose of olanzapine optimized to 25 mg/day. However, her symptoms did not improve. Therefore, olanzapine was cross-tapered with haloperidol (reaching 10 mg, twice/day). The patient refused the possibility to start her in long-acting antipsychotic. She was discharged two months later, with prescriptions for haloperidol and procyclidine (5 mg, as need) and continued to receive care in an outpatient clinic.

After five weeks, her psychotic symptoms worsened, and she presented to the emergency department with delusions of persecution toward her family and auditory hallucinations. Since her psychotic symptoms remained unresolved after olanzapine and haloperidol, she was readmitted with an updated diagnosis of treatment-resistant schizophrenia, which is most often treated with the antipsychotic clozapine. At this time, the patient underwent a biochemical analysis, an ECG, and a basic physical examination. Author confirmed that the results of these clinical investigations all fell within the healthy range and that the patient had no history of cardio-metabolic disease or other risk factors prior to initiating clozapine treatment. The dose of clozapine Initiated at 12.5 mg at night then increased on the next day to 12.5 mg twice/day. During that day, the patient did not complain of any symptoms; however, a routine check of her vital signs revealed an increased heart rate.

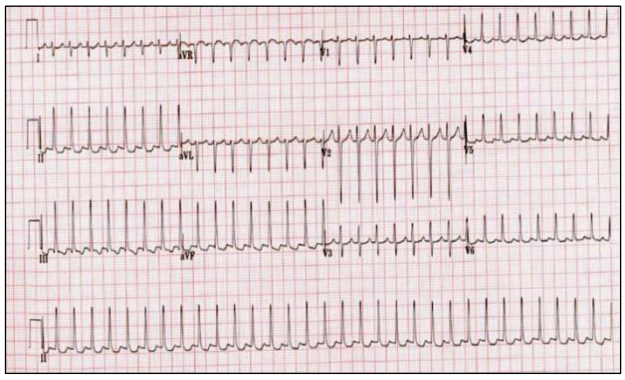

Figure 1: Supraventricular tachycardia with regular rhythm and heart rate of 191 bpm. Narrow QRS complex and no visible P wave.

The ensuing ECG was suggestive of SVT (Figure 1) with a heart rate of 191 beats/min. Cardiologist opinion was sought and SVT was terminated with 6 mg intravenous (IV) push of adenosine into sinus tachycardia at 120 bpm.

Further examination confirmed the presence of tachycardia and established that the patient did not have chest pain, dyspnea upon exertion, fever, or general malaise. Additional clinical indicators, including thyroid function, erythrocyte sedimentation rate, and C-reactive protein levels, were within the healthy range and no findings were suggestive of ischemic heart disease or cardiomyopathy. Cardiologist opinion concluded that the patient was likely experiencing a clozapine-related adverse reaction and clozapine treatment was stopped immediately. The patient was kept under close observation with a daily ECG and hourly monitoring of her vital sings. One day after clozapine treatment was discontinued, the patient's pulse rate returned to 81 bpm. As an alternative treatment, author administered amisulpride (50 mg, twice/day) to manage the patient's psychotic symptoms. The dose was gradually increased as guided by symptom assessment and reached 600 mg twice/day within two months.

In May 2017, after two weeks of discharge, she readmitted to the psychiatric unit with worsening of her psychotic symptoms due to poor response to her medications associated with irritability, agitation, low mood, lack of interest and hopelessness. After assessment of patient condition, author considered restarting the clozapine therapy as the treatment trail of amisulpride failed.

After assessing the patient's condition, restarting the clozapine therapy seemed to be the best therapeutic option. A cardiology consultation was sought regarding the safety of resuming clozapine treatment. After an ECG showed healthy cardiac activity and a thorough risk/benefit analysis, the decision was made to re-challenge with clozapine in combination with verapamil (40 mg twice/day) with close monitoring of the patient's vital sings. Amisulpride was cross-tapered till discontinuation and clozapine was titrated up to a dose of 400 mg at night over a three-week period. Fortunately, the patient was tolerated clozapine very well.

Clozapine level was obtained at dose 400 mg/Hs and the result show 2831 mcg/l (normal levels 350-650 mcg/L), so the dose reduced to 300 mg/Hs with a level equal to 1900 mcg/l. The dose farther reduced till adjusted to be 75 mg/Hs with a level equal to 429 mcg/l. Four months after admission, the patient was discharged in a stable, controlled condition with some hallucinatory gestures.

DISCUSSION

In this report, author have described a case in which a low dose (25 mg/day) of clozapine resulted in SVT merely two days after treatment initiation. Other potential

causes, such as myocarditis, cardiomyopathy, or neuroleptic malignant syndrome were ruled out since the absence of the symptoms with normal cardiac markers and rapid resolve of tachycardia following clozapine cessation.[8,9]

In contrast to this case, most of the previously-reported ones presented with tachycardia at clozapine doses over 50 mg.[10-15] The only exception, 37.5 mg/day, still greatly exceeded the dose described here.[16] Furthermore, the onset of tachycardia in those cases ranged from five days to two months after clozapine initiation, much longer than two days observed in this case. In terms of the nature of the ECG finding specifically, the majority of the previously reported cases exhibited sinus tachycardia. Only a few presented with SVT and these were mainly dose-dependent and involved rapid titration.[10-16] However, in this case, SVT developed early (two days) after a low dose of clozapine (25 mg) was slowly titrated. In the present case, the calcium channel blocker verapamil was chosen to supplement clozapine due to its proven ability to suppress tachycardia and to augment neuroleptics in patients with schizophrenia.[17] Other pharmaceutical options (e.g., BB) were not considered due to associations with increased risk of agranulocytosis, dyslipidemia and depression.[18,19]

Author could not find any controlled, randomized trials on the pharmacological treatment of clozapine-induced tachycardia to guide the decision.[20] However, some small-scale interventions have reported success, including two independent case reports that both used verapamil to treat clozapine-induced tachycardia.[11,13] Additionally, in a case series with two patients, clozapine-induced tachycardia was effectively resolved using ivabradine, this novel compound is intended to regulate heart rate and represents an alternative option for patients who are intolerant to β blockers.[12] Overall, this area remains largely clinically unexplored and large-scale studies on the management of clozapine-induced tachycardia are needed. The effective management of adverse side effects, such as clozapine-induced tachycardia, will greatly improve the outcome and quality of life for patients with schizophrenia and reduce the premature clozapine discontinuation.[21] Toward this end, controlled, large-scale, randomized studies are required to determine optimal pharmacological combinations and treatment regimens.

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