PSYCHOLOGICAL MEDICINE

Combined Aripiprazole and Electroconvulsive Therapy in a Patient with Treatment-Resistant Schizophrenia and QT Prolongation

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ABSTRACT

Introduction: **Clozapine is regarded as the most effective antipsychotics for patients with treatment-resistant schizophrenia. Of late cardiac safety becomes a principal concern including QTc prolongation that can lead to sudden cardiac death.**

Objective: **This case report will highlight the development of clozapine-induced QTc prolongation, and subsequent stabilization with combined aripiprazole and electroconvulsive therapy (ECT) in a patient with treatment-resistant schizophrenia.**

Result: **We reported a 30-year-old male patient with treatment-resistant schizophrenia who developed QTc prolongation. In 2014, prolonged QTc 521ms was attributed to hypocalcemia. Then in 2016, prolonged QTc 492 ms was noted after the ECT, and most recently QTc 504 ms while on clozapine 100 mg daily. Other investigations including electrolytes, echocardiogram, thyroid, renal and liver function tests were normal. Subsequently, the patient was stabilized on combined aripiprazole and ECT. The QTc ranged 460 to 494 ms while he was on aripiprazole 15 mg daily.**

Conclusion: **The combined use of aripiprazole and ECT is safe for treatment of treatment-resistant schizophrenia with prolonged QTc. Close monitoring is recommended since QTc impact of aripiprazole may be additive to the arrhythmia risk.**

KEY WORDS

aripiprazole, electroconvulsive therapy, QT prolongation, clozapine, schizophrenia

INTRODUCTION

To date clozapine is the most effective antipsychotic for patients with schizophrenia who are treatment resistant[1,2)]. A systematic review and meta-analysis revealed a 40% response rate to clozapine[2)] and lower mortality rate among clozapine-treated individuals with treatment-resistant schizophrenia compared to individuals not treated with clozapine[3)].

Of late cardiac safety becomes a principal concern as emerging data show second generation antipsychotics such as clozapine, contributed to the increased mortality due to the association with life-shortening metabolic adverse effects, including weight gain, dyslipidemia, and type 2 diabetes mellitus[4,5)]. Additionally, cardiac adverse effects like myocarditis[6,7)], pericarditis[8,9)], and cardiomyopathy[10)] had been reported as well.

Of particular interest is clozapine effect on QTc prolongation (> 450 ms in males, > 470 ms in females) which put patients at risk for sudden cardiac death. Prolongation of ventricular action potential duration may result in polymorphic ventricular tachycardia termed torsade de pointes that can degenerate into ventricular fibrillation. A QTc values higher than 500 ms are strongly prolonged and linked with a clear risk of torsade de pointes[11)].

However, QTc prolongation alone does not appear to explain torsade de pointes; several other factors must be present simultaneously with QT prolongation before torsade de pointes occurs[12)]. A systematic review of 10 observational studies with a total of 89,532 patients concluded that risk factors for QTc prolongation evidence were very strong for hypokalemia and medication such as diuretics, antiarrhythmic drugs. The evidence was strong for age ≥ 65 years, female gender, smoking, ischemic cardiomyopathy, hypertension, arrhythmia, thyroid disturbances, hypocalcemia and use of ≥ 1 QTc-prolonging drugs[11)].

This case report will highlight the development of clozapine-induced QTc prolongation, and subsequent stabilization with combined aripiprazole and electroconvulsive therapy (ECT) in a patient with treatment-resistant schizophrenia.

CASE REPORT

A 30-year-old, single, unemployed gentleman with schizophrenia on oral clozapine 100 mg daily was admitted to psychiatric ward with auditory hallucinations, grandiose delusions, insomnia, disorganized behavior and irritability for 2 weeks duration in March 2017. It was noted that the patient had asymptomatic prolonged QTc 504 ms. Other investigations including electrolytes, echocardiogram, thyroid, renal and liver function tests were normal.

Due to the QTc prolongation, he was referred to medical and cardiology team and was treated as prolonged QTc secondary to clozapine. The clozapine was then withheld and patient was restarted on aripiprazole which was optimized up to 15 mg daily. The patient showed improvement in the ward, however, he was readmitted again 2 weeks after discharge as he developed similar episode of auditory hallucinations and disorganized behavior. For that admission he was started on acute ECT for 12 sessions in a closely monitored setting by anesthesia team while aripiprazole was continued at 15 mg daily. The patient showed tremendous improvement, thus fortnightly maintenance ECT

Received on August 28, 2017 and accepted on December 17, 2017

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was planned. He was well and able to participate in occupational therapy activities. The QTc ranged 460 to 494 ms while he was on aripiprazole 15 mg daily. However, he received only 2 sessions of maintenance ECT and was lost to follow-up.

Past psychiatric history revealed that the patient was diagnosed with schizophrenia 10 years before when he presented with auditory hallucinations, persecutory delusions, social withdrawal and poor self-hygiene of 6 months duration. He had been frequently admitted and treated with multiple psychotropic agents such as olanzapine up to 20 mg daily, quetiapine up to 600 mg daily, sulpiride 800mg daily, lithium 600 mg daily, intramuscular depot flupenthixol 40 mg monthly and aripiprazole up to 15mg daily, however, patient did not show much improvement. He was then treated as a case of treatment resistant schizophrenia and started on clozapine, and the highest dose that he had ever been on was 500 mg daily. He was also given a few courses of acute electroconvulsive therapy (ECT). However, the clozapine regime had to be restarted a few times as the patient defaulted treatment once he felt better during periods of partial remission. He also had 2 episodes of prolonged QTc; in 2014, 521 ms, which was attributed to low serum calcium level, 2.07 mmol/L (normal value 2.2-2.6 mmol/L), during this time, patient defaulted treatment for more than a month prior to admission, and in 2016, QTc was 435 ms on admission but was prolonged to 492 ms after 4th session of acute ECT, patient at the time was on olanzapine 20mg daily which was started 2 months prior to the admission. For both of these episodes, the patient was referred to medical team for assessment.

DISCUSSION

In this patient, aripiprazole was chosen as it confers the lowest risk of QTc prolongation. A meta-analysis[13] revealed that the QTc prolongation risk with aripiprazole was lower compared with placebo and other antipsychotics including chlorpromazine, clozapine, haloperidol, olanzapine, perospirone, perphenazine, quetiapine, risperidone, sulpiride, and ziprasidone, and thus concluded that aripiprazole has a low cardiac risk in healthy patients. Nevertheless, the authors cautioned that the small but measurable QTc impact of aripiprazole may be additive to the arrhythmia risk in patients at high risk for torsade de pointes.

Reversible ECG changes had been reported in a patient who developed first degree AV block with aripiprazole 45 mg monotherapy. Two other patients developed left bundle branch block with concomitant use of risperidone and clonezepam, respectively[14]. A study by Nagamine[15], identified polypharmacy and high doses of more than 1,000 mg chlorpromazine equivalent as risk factors among 12 mortality cases related to aripiprazole long acting injection in Japan. Therefore, monitoring of high risk patient on aripiprazole is important. Of note, this patient had history of hypocalcemia in 2014 which may recur in future while the patient on aripiprazole.

Recently, it was found that antipsychotics with a high potency for the hERG potassium channel blockade, a well-known mechanism involved in drug-induced arrhythmia[16], had a higher risk of ventricular arrhythmia and/or sudden cardiac death, regardless of cardiovascular disease status[17]. A systematic review[18] concluded that aripiprazole, clozapine, droperidol, mesoridazine, olanzapine, perphenazine, risperidone, and thioridazine have evidence of hERG liability.

Since the patient was previously on combined antipsychotics and ECT, it was only logical that aripiprazole should be augmented with ECT. The safety of the electroconvulsive therapy-aripiprazole combination was reported in previous studies[19-21]. This patient was planned for maintenance ECT; however he defaulted after 2 sessions. The use of maintenance ECT combined with antipsychotics is a good treatment strategy in treatment-resistant psychosis. A recent case report described a patient with treatment-resistant psychosis with neurosyphilis who had received more than 120 maintenance ECT sessions while receiving clozapine[22].

CONCLUSION

The combined use of aripiprazole and ECT is safe for treatment of treatment-resistant schizophrenia with prolonged QTc. Close monitoring is recommended since QTc impact of aripiprazole may be additive to the arrhythmia risk.

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