

A prospective study on change of QTc interval with antipsychotic medications in patients of schizophrenia and related psychotic disorder



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ABSTRACT

Background: Sudden unexplained death in individuals with mental health problems was described in 1960 and a link with antipsychotic drugs was postulated over 40 years ago. Down the years, a clear relation between electrocardiography (ECG) abnormalities and antipsychotic use was observed with special emphasis on QT prolongation. Various factors modulate the risk of QT prolongation including gender, age, race, and drug choice. An evaluation of antipsychotic use-induced QT changes in Eastern Indian population is the dire need of the hour. **Aims and Objectives:** The aim and objective are to study the effects of risperidone, olanzapine, and aripiprazole on QT interval after a period of 4 weeks of usage in previously drug-naïve Eastern Indian psychotic patients. **Materials and Methods:** A total of 78 drug-naïve patients fulfilling inclusion and exclusion criteria were randomly assigned to receive risperidone, olanzapine, and aripiprazole after a baseline ECG. A repeat ECG after 4 weeks of drug usage was done and compared using standard protocols with respect to QT interval. Findings were tabulated and statistical analysis was done using SPSS 25.0 to test for statistical significance at $P < 0.05$. **Results:** Our study found significant rise in QT values after 4 weeks of using olanzapine and aripiprazole, but not with risperidone. However, none of the patients from either of the groups experienced any incidence of QT prolongation. Rise with olanzapine was significantly higher than that with risperidone. **Conclusion:** Caution is suggested in patients with risk factors for QT prolongation or a high value of QT during prescribing olanzapine. Studies with larger sample size can be carried out to find genetic predisposition of Indian population to anti-psychotic induced QT interval rise/prolongation.

Key words: Aripiprazole; Olanzapine; QT interval; Risperidone

INTRODUCTION

Sudden unexplained death in individuals with mental health problems was described in 1960 and a link with antipsychotic drugs (APD) was postulated over 40 years ago.¹ Down the years, a clear relation between electrocardiography (ECG) abnormalities like QT prolongation and Torsades de pointes (TDP-an atypical polymorphic tachycardia) and antipsychotics have been established leading to the subsequent withdrawal of number of antipsychotics.²

The QT interval provides a measure of the time interval between the start and the end of the electrical activation of the ventricles of the heart. QTc are usually around 400 ms and values lesser than 450 ms are considered normal. QTc values >450 ms in men and 460 ms in women are generally considered prolonged.³ Although a number of studies investigate the congenital and acquired⁴ forms of QT prolongations and change in susceptibility with genes,⁵⁻⁸ race,⁹ polypharmacy,¹⁰ yet till date no such study has been conducted amongst Eastern Indian population assessing effects of antipsychotics on QTc interval. Our study aims to bridge this gap.

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Aims and objectives

To study the effects of Risperidone, Olanzapine, Aripiprazole on QT interval after a period of 4 weeks of usage in previously drug naïve Eastern Indian psychotic patients.

MATERIALS AND METHODS

The current study was conducted in a tertiary center from Eastern India. The study obtained ethical clearance from the institutional ethics committee (Ref No.-MC/KOL/IEC/NON-SPON/201/12-2018). The study duration was 1 year (January 2019–January 2020).

The sample size was calculated taking confidence level as 99%, margin of error as 5%, and population proportion as 0.03, according to a previous study which found that 3% of patients receiving APD¹¹ developed prolonged QT interval.

78 patients were purposively sampled if they fulfilled the following inclusion criteria, i.e. (a) drug-naïve patients, (b) age 18–65 years, (c) ability to comprehend and converse in English/Bengali/Hindi, (d) willing to participate, follow-up, and give informed consent. Patients refusing to give consent or having known cardiological morbidity, substance abuse, electrolyte disturbances, being measured at the beginning of the study, or taking other psychotropics or drugs causing cardiological morbidity were excluded. Sampled patients were randomly assigned to receive different antipsychotic drugs. A baseline 12-lead ECG with long lead II was done for each patient. The ECG was repeated after 1 month of drug use.

QT interval was measured from the onset of the QRS complex to the offset of the T wave, defined as the deflection of T wave when it returns to the isoelectric line or as the nadir between the T and U waves. The interval was measured in 3 successive beats in the lead II and a mean QT was calculated. QT was converted to QTc using the Framingham heart formula ($QTc = QT + 0.154[1 - RR]$), RR being the time between beats representing the heart rate. In accordance with the original definition of prolonged QTc and previous studies, we defined QTc prolongation as QTc values >450 ms in men and 460 ms in women.³

For statistical analysis, descriptive statistics were expressed in terms of percentage and mean with standard deviation. Analytical statistics were done by paired t-test, analysis of variance (ANOVA), and multiple comparison tests.

RESULTS

Out of 78 participants, 32 were females and 46 were males (Figure 1). Out of 78 patients, 26 patients (33.3%) received

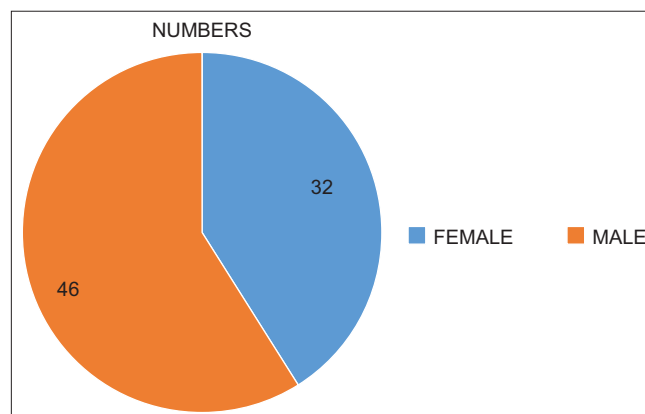


Figure 1: Distribution of study population based on gender

Table 1: Drug-based distribution of patients (n=78)

Drugs	Frequency (%)
Olanzapine	26 (33.3)
Risperidone	28 (35.9)
Aripiprazole	24 (30.8)
Total	78 (100.0)

olanzapine, 28 patients (35.9%) received risperidone, and 24 patients (30.8%) received aripiprazole (Table 1). Mean age of participants was 29 years for olanzapine, 32 years for risperidone, and 31 years for aripiprazole. Groups were comparable with respect to age and gender.

Out of 78 patients, 52 patients showed a rise in QT but none fulfilled the criteria for QT prolongation. With olanzapine use 21 out of 26, with risperidone 13 out of 28, and with aripiprazole 18 out of 24, patients have shown a rise in QT values.

Paired t-test was used for QT measurements before and after the use of drugs. Mean QT before drug use was 380 ± 31.604 ms. Mean QT post-drug use was 393.56 ± 23.281 ms. The rise was inferred to be significant with $P=0.000$. Mean QT before olanzapine use was 366.23 ± 27.195 ms. Mean QT post-drug use was 393.38 ± 29.948 ms. The rise was inferred to be significant with $P=0.000$. Mean QT before risperidone use was 393.14 ± 23.496 ms. Mean QT post-drug use was 393.82 ± 23.724 ms. The rise was inferred to be not statistically significant with $P=0.915$. Mean QT before aripiprazole use was 380.40 ± 25.794 ms. Mean QT post-drug use was 394.20 ± 13.605 ms. The rise was inferred to be significant with $P=0.000$ (Table 2).

The difference in QT changes between drug groups was inferred to be significant using ANOVA ($P=0.006$). Multiple comparison tests revealed a statistically significant difference between groups using olanzapine and risperidone (Table 3).

Table 2: QT rise among various drug users along with P-values

Drug name	Total number	Mean QT pre (ms)	Mean QT post (ms)	QT rise, n (%)	P-value
Olanzapine	26	366.23±27.195	393.38±29.948	21 (19.2)	0.000
Risperidone	28	393.14±23.496	393.82±23.724	13 (46.4)	0.915
Aripiprazole	24	380.40±25.794	394.20±13.605	18 (75)	0.000

Table 3: Comparison of QT change between various drug groups

Drug (I)	Drug (J)	Mean difference (I-J)	SE	Significance P<0.05
Olanzapine	Risperidone	23.618*	7.118	0.004
	Aripiprazole	14.696	7.398	0.152
Risperidone	Olanzapine	-23.618*	7.118	0.004
	Aripiprazole	-8.923	7.271	0.671
Aripiprazole	Olanzapine	-14.696	7.398	0.152
	Risperidone	8.923	7.271	0.671

SE: Standard deviation

DISCUSSION

TDP, from the French for “twisting of the points,” is an atypical ventricular tachycardia characterized by oscillations of the points or peaks (“pointes”) around the main axis of the ECG, giving rise to a unique morphology. The systemic review of literature extending from 2000 to 2007 by Serge Sicouri and Charles Antzelevitch examining the mechanisms and predisposing factors underlying the development of cardiac arrhythmias and sudden cardiac death among antipsychotic and antidepressant drugs in clinical use, inferred that TDP can be caused by either congenital or acquired long QT syndrome (LQTS). Acquired LQTS refers to a syndrome similar to the congenital form but caused by exposure to drugs that prolong the duration of the ventricular action potential or secondary to cardiomyopathies or associated with bradycardia or electrolyte imbalance.⁴ The acquired form of the disease is far more prevalent than the congenital form and in some cases, may have a genetic predisposition. Risk factors include female gender, age, bradycardia, metabolic inhibitors, hypokalemia, hypomagnesemia, drug overdose, and co-administration of QT-prolonging drugs. Another observation from the review was APD generally have a higher torsadogenic potential (Category 1 and 2) than antidepressants (Category 4) which are more typically observed in the presence of drug combinations. Available data suggest that up to 10–15% of individuals who develop TDP following exposure to QT-prolonging drugs possess mutations associated with the LQTS and may be considered to have a subclinical form of the congenital syndrome.^{4,5}

Abbott et al.,⁶ were among the first to show that a polymorphism (a genetic variation that is present in >1% of the population) in an ion channel gene is associated

with a predisposition to drug-induced TDP. Yang et al.,⁷ showed that DNA variants in the coding regions of genes predisposing to acquired LQTS can be identified in ~ 10–15% of affected subjects. Splawski et al.,⁸ further advanced this concept by identifying a heterozygous polymorphism among Africans and African Americans, which increases the risk for acquired TDP.

In 2013, Manini et al., carried out a study assessing racial susceptibility inferring that racial susceptibility is more important than drug class in determining an individual patient’s risk of QT prolongation after acute drug overdose.⁹ Elliott et al., observed no difference in average QTc interval for the whole sample of patients receiving no antipsychotics, antipsychotic monotherapy, or antipsychotic poly-pharmaceutical treatment.¹⁰ Khan et al., pointed out that QT-DDIs were significantly associated with 6–7 prescribed medications.¹² Spellmann et al., did a study on QTc prolongation and showed a significant overall influence of SCN5A (H558R) on QTc duration but no significant interaction with antipsychotic treatment.¹³

Our study found significant rise in QT values after 4 weeks of using olanzapine and aripiprazole, but not with risperidone. However, none of the patients from either of the groups experienced any incidence of QT prolongation. In general, both olanzapine and risperidone are considered safe drugs when considered with respect to the chances of QT prolongation.^{14,15} Our study asserts no incidences of QT prolongation with risperidone, olanzapine, and aripiprazole. However, although risperidone does have evidence of incidences of QT prolongation,¹⁵ in our study, the rise with olanzapine was significantly higher than that with risperidone. The result persisted after age and gender count was comparable among the 2 groups. There are no studies in Indian population available to compare these results with. This difference can be implicated to the genetic predisposition of the population. As in one previous study, it has been inferred that the genetic constitution is the more important determining factor behind cases of drug-induced QT prolongation.⁶ This warrants overall risk assessment, continuous electrocardiographic monitoring as per clinician’s discretion, and search for safer alternatives in high-risk individual¹⁶ before initiating antipsychotic therapy. Appropriate dosing of anti-psychotic medications is also important in averting ECG abnormalities.¹⁷ Studies with aripiprazole are significantly scarce. Although no study

focused on QT prolongation with aripiprazole was found, a meta-analysis revealed that the mean Δ QTc interval was decreased with aripiprazole and QTc prolongation risk was lower compared with placebo and active controls.¹⁸ A similar cardiac safety profile with aripiprazole has been assessed in another meta-analysis study.¹⁹

However, our study has its limitations in the form of small sample size and short follow-up duration. Furthermore, our study was hospital based and thus sample might be different from actual community.

Limitations of the study

This study was conducted on a small sample and henceforth needs to be replicated in larger samples for extrapolation of the results.

CONCLUSION

Our study found a significant rise in QT values after using olanzapine and aripiprazole but not with risperidone. However, none of the patients experienced QT prolongation. Caution is suggested in patients with risk factors for QT prolongation or a high value of QT during prescribing olanzapine. Studies with larger sample size can be carried out to find genetic predisposition of Indian population to anti-psychotic induced QT interval rise/prolongation.

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