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Risperidone and Corrected QT-interval Prolongation in Surface Electrocardiogram

[1]F. Ranjbar, [2]F. Akbarzadeh, [2]N.M. Ahmadi and [2]M. Abbasnejhad
[1]Clinical Psychiatry Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Cardiology, Cardiovascular Research Center,
Tabriz University of Medical Sciences, Tabriz, Iran

Abstract: Risperidone is an antipsychotic medication suspected of causing QT prolongation and several cases are reported in this regard. However, available information with respect to its effect on QT interval is limited especially from different settings. The aim of this study was to assess the effect of risperidone in lengthening QT interval among psychotic patients referred to a psychiatric ward in North West of Iran. A controlled cohort study was conducted on psychotic patients referred to Razi Hospital from April 2010-2011. The treatment cohort groups were 120 patients receiving risperidone for the first time during their treatment. The comparison cohort included 60 control patients who were not receiving risperidone. An electrocardiogram was obtained from all the study participants at admission time, one week afterwards and at discharge. Corrected QT interval (QTc) was determined using Bazett's formula. QTc dispersion was calculated as Max_{QTc}-Min_{QTc}. Data were analyzed using SPSS statistical software package. The mean change in QTc measures over time was not statistically significant in control group. However, QTc increment was statistically significant over time in V1 and V3 leads in risperidone group. Multivariate longitudinal data analysis, using between-effects model, to manage multiple measurements over time found the overall QTc trend to be different between the groups ($p<0.01$). Risperidone may have significant effects on QT interval and QT dispersion. Physicians and psychiatrists should be aware that prolonged QTc interval is a potential indicator of cardiovascular risk and should be cautious in prescribing potentially QT-prolonging medications, at least to certain patients.

Key words: Risperidone, antipsychotic drugs, arrhythmia, side effects, electrocardiogram, atypical antipsychotics

INTRODUCTION

The QT interval is defined as a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. It was in 1957 that the first case of Long QT syndrome (LQTS) was presented from Norway (Jervell and Lange-Nielsen, 1957). It is characterized by a prolonged QT interval in the electrocardiogram, syncope and sudden cardiac death due to ventricular tachyarrhythmias, typically torsades de pointes (Morita *et al*., 2008). The QT interval is the duration of ventricular depolarization and repolarization, caused by trans-membrane flow of ions. It should be taken into account that QT interval prolongation is not necessarily associated with torsades de pointes. Other etiologies include antiarrhythmic drugs such as amiodarone and procainamide (Bernardi *et al*., 1998; Welch and Chue, 2000). Potential lengthening of the QT interval induced by atypical antipsychotic drugs have been the source of much concern, nevertheless, the conventional antipsychotic medications available nowadays are significantly more cardiotoxic, particularly agents in the butyrophenone and phenothiazine classes (Welch and Chue, 2000). These effects may be significant in the presence of predisposing factors. Risperidone is an antipsychotic medication suspected of causing QT prolongation and several cases are reported in this regard. However, available information with respect to its effect on QT interval is limited especially from different settings (Campbell *et al*., 1999; Suzuki *et al*., 2012). The aim of this study was to assess the effect of risperidone in lengthening QT interval among psychotic patients referred to a psychiatric ward in North West of Iran.

Corresponding Author: F. Akbarzadeh, Department of Cardiology, Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

MATERIALS AND METHODS

A controlled cohort study was conducted on psychotic patients referred to Razi Hospital from April 2010-2011. All the patients were admitted to Psychiatry Ward of the Razi Hospital in Tabriz, Iran. The treatment cohort groups were 120 patients receiving risperidone for the first time during their treatment. The comparison cohort included 60 control patients who were not receiving risperidone. The comparative group was made up of psychiatric patients presumed of lacking changes in their medication during the course of the study. They were frequency matched for gender and age. Both the test and control group lacked a known history of cardiovascular diseases or electrolyte imbalance disorders. Patient received a dose of 3-8 mg risperidone based on clinical decision making. An electrocardiogram was obtained from all the study participants at admission time, one week afterwards and at discharge. QT interval was measured using 10X zoom screen caliper software. Measurements were done by two electrophysiology nurses trained for this purpose with good pretested inter-rater reliability to ensure reproducibility of measurement. They were kept blind to study purpose and patient grouping. A pilot assessment reliability study was conducted on 10 patients showing appropriate inter-rater agreement between the nurses. Measurements were done on three precordial leads (V1, V3 and V5) and three limb leads (I, aVR and aVF). In three consecutive cycles with stable baseline without noise, QT measurements were averaged to represent QT interval in that lead. QTc was determined using Bazett's interval" formula (Bazett, 1920):

$$QTc = \frac{\text{QT duration}}{\sqrt{PR}}$$

where, PR is the interval between wave P and wave R in electrocardiogram, QTc dispersion was calculated as:

$$\text{QTc dispersion} = Max_{QTc} - Min_{QTc}$$

Statistical analysis: Data were entered into computer and analyzed using SPSS statistical software package version 16. Bivariate tests such as t-test and chi-square test, as well as longitudinal multivariate data analysis were used. A p-value lower than 0.05, was considered as statistical significance.

Study protocol was approved by the regional committee of ethics in Tabriz University of Medical sciences. Written informed consent was obtained from all guardians legally responsible for giving consent as well as those patients who were not psychotic at the time of recruitment.

Patients with following conditions were excluded from the study:

- Hypokalemia, hypocalcaemia, or hypomagnesaemia at baseline assessments
- History of malignancy
- History of using amiodarone, antiretroviral agents, antifungal agents, quinolone antibiotics, antiarrhythmic medications and risperidone

RESULTS

Groups had equal distribution according to gender. Patients in treatment group were a bit older but had lower diastolic blood pressure, systolic blood pressure and lower heart rate. Mean body mass index was similar between groups. Further details are presented in Table 1. The mean change in QTc measures over time was not statistically significant in control group. But QTc increment was statistically significant over time in V1 and V3 leads risperidone group. Descriptive statistics of QTc measurements and bivariate between-group comparison test results at each time point are given in Table 2. Contrary to RR, the QTc change trend was found to have significantly different slopes between the two groups. It can be found in this table that prolonged QTc was observed more in risperidone group mostly after one week of treatment and after discharge.

The correlations among QTc measures on different leads can be assessed in Fig. 1. It can be seen that QTc measurements in various cardiac leads are highly correlated in pairs. The Risk Ratios (RR) of having QTc>450 at discharge time for those using risperidone over control group were 1.08, 1.2 and 1.2, respectively for V1, V3 and V5 leads. None of the RRs were statistically different from 1 as null effect.

Multivariate longitudinal data analysis, using between-effects model, to manage multiple measurements over time found the overall QTc trend to be different between the groups ($p<0.01$).

Table 1: Background variables compared between the two study groups

Variables	Cases	Controls
Gender	60 males and 60 females[#]	30 males and 30 females[#]
Age (years)	39.6±11.1	35.9±10
Mean systolic blood pressure (mmHg)	103.3±11.4	114.3±10.3
Mean diastolic blood pressure (mmHg)	66.3±7.5	68±6.3
Mean heart rate count (beats)	73.9±7.2	77.9±6.1
Mean body mass index (kg m^{-2})	24.6±2.7	24±3.2

Values are Mean±SD, [#]values are in numbers

Table 2: Electrocardiographic measures compared between groups at three time points

	Baseline			Week 1			Discharge		
Measure	Control	Risperidone	p-value	Control	Risperidone	p-value	Control	Risperidone	p-value
R-R V6	757.57±150.4	745.47±162.5	0.6	784.15±173.2	756.18±165.6	0.3	792.67±172	768.10±187.6	0.4
QTc-V1	417.23±29.7	417.42±27.1	0.9	414.18±23.14	423.38±29.1	0.04	414.29±32.2	424.18±27.6	0.003
QTc-V3	419.60±27.7	424.13±28.8	0.001	416.75±35.1	433.37±27.6	0.001	415.92±34.6	436.75±28.9	0.005
QTc-V5	424.96±31.1	431.69±28.12	0.1	423.99±33.0	431.40±27.5	0.1	423.44±32.7	432.77±30.1	0.05
QTc-I	415.10±25.2	420.08±30.0	0.3	414.03±28.6	417.71±27.8	0.4	414.05±3.7	420.69±32.2	0.2
QTc-avF	417.71±30.8	425.59±28.5	0.06	410.42±29.2	428.54±29.2	0.001	410.70±28.9	426.28±31.3	0.001
QTc-avR	407.68±24.5	417.80±26.3	0.01	410.12±30.0	420.42±27.5	0.02	409.61±30.1	420.12±30.4	0.02
QTD	46.26±20.3	051.16±18.4	0.1	45.44±13.3	53.06±41.6	0.04	42.49±19.3	51.92±18.7	0.002
QRS duration	77.36±13.4	077.57±16.4	0.9	78.33±13.3	77.96±14.5	0.9	79.31±12.5	76.76±14.6	0.2
PR interval-V6	144.90±20.5	145.60±21.7	0.8	144.23± 20.8	146.43±21.3	0.5	144.12±17.9	143.5818.2	0.8

Values are Mean±SD, V(1,3,5): Chest leads in electrocardiogram, avF and avR: Two of the augmented limb leads in electrocardiogram

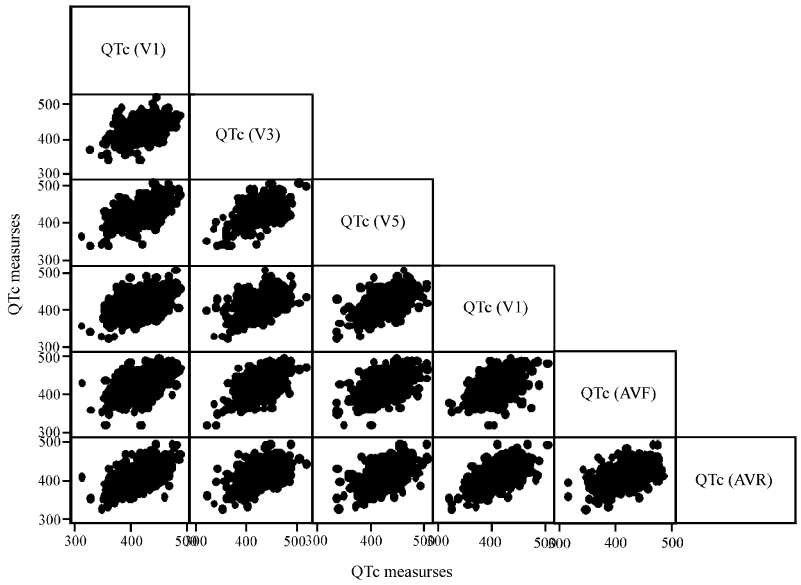

Fig. 1: Scatter plots of the QTC measures on different leads of electrocardiogram from patients receiving risperidone for the first time in Razi Hospital, Tabriz, Iran, V (1,3,5): Chest leads in electrocardiogram, avF and avR: Two of the augmented limb leads in electrocardiogram

DISCUSSION

Long QT syndrome (LQTS) was initially described as a rare inherited disease, a known cause of sudden death due to torsades de pointes, but many patients were later identified and the mechanisms responsible for tachyarrhythmias are common to other sudden death syndromes (Morita *et al*., 2008).

Risk factors of prolonged QTc interval are studies both in general populations and specific disease groups (Benoit *et al*., 2005; Brown *et al*., 2001; Giunti *et al*., 2007; Grandinetti *et al*., 2005; Reinsch *et al*., 2009). In a large national health survey in USA 8561 subjects over 40 years of age, underwent an electrocardiographic examination through which age, female sex, hypocalcemia (men), hypokalemia (women) and a history of thyroid disease and myocardial infarction (men) were found to be associated with a prolonged QTc interval. Also, taking QT-prolonging medications was associated with increased odds of prolonged QTc interval in both men and women (Benoit *et al*., 2005; Huq, 2007). Nevertheless, another American cohort also suggested that genetic factors may play an important role in determining QTc interval length than conventional biochemical and metabolic CVD risk factors (Grandinetti *et al*., 2005).

Antipsychotics are not always harmless medications. Other than its well knows side effects it may affect lipid profile it have even been reported to cause priapism. Also, these drugs are not made only for psychotic diseases (Idonije *et al*., 2012; Hosseini and Polonowita, 2009; Kilic *et al*., 2012). Some antipsychotics are shown to be associated with QTc prolongation.

However, methodological considerations preclude considering any antipsychotic to be free of the risk of QTc prolongation and dysrhythmia (Taylor, 2003).

Ravina *et al.* (2007) described full exposure of an acquired Long QT Syndrome in an elderly female patient on long-term risperidone treatment just when bradycardia due to complete AV block developed. They stated that a combined block of the rapid and delayed components of the Ik current and concluded that risperidone should be used with caution in female patients prone to bradycardia (Ravina *et al.*, 2007). Other cases are also reported in literature. Goyal and Goyal (2003) reported a case of symptomatic bradycardia secondary to risperidone in a young man undergoing alcoholic withdrawal. This occurred after moderately high levels of risperidone. Later in 2004 another case was described of acute sinus bradycardia with frequent premature ventricular bigeminy complexes in a geriatric patient taking an initial low starting dose of risperidone. He had normal sinus rhythm before the risperidone was started (Tran *et al.*, 2004).

In a randomized clinical trial risperidone was compared with aripiprazole and placebo for efficacy. However, the researchers also compared QTc in risperidone with placebo. In their study three out of 100 patients in risperidone group developed QTc prolongation (QTc>450 or 10% increase in QTc compared to baseline), while, no one in aripiprazole or placebo groups developed such an event. The difference was not statistically different (Potkin *et al.*, 2003). Considering the figures provided by the authors, the main explanation could be sought in low statistical power of the trial. Similarly in our study using dichotomized assessments, prolonged QTc was observed more in risperidone group without statistical significance. Due to low incidence of the event the study turns underpowered, but as found in our results, using longitudinal multivariate analysis found the trend of QTc change over time to be statistically different between groups.

In line with our hypothesis, animal studies have shown that risperidone is a potent IKr blocker. It prolongs cardiac repolarization at clinically relevant drug concentrations and should not be considered a no-risk alternative to older neuro leptic agents (Drolet *et al.*, 2003). Therefore, clinical attention to QT prolongation should be warranted when prescribing risperidone.

Similarly, with previous studies we used Bazett's formula to adjust the QT interval. The QT interval varies with heart rate, becoming shorter as heart rate increases. Various correction factors have been suggested, the most commonly used being Bazett's correction which has a wide acceptability. However, the effect of drug itself on heart rate should be considered in interpreting the results (Malik and Camm, 2001). Results of this research provided consistent information that can be of help in improving the generalizability of available evidence considering the higher variability of clinical settings. To provide more reliable and beneficial evidence with equivalent applicability to various clinical settings, future research in recommended to focus on precision improvement considering larger scale studies, external validity improvement targeting higher heterogeneity of various clinical setting as well as long-term effectiveness studies. Investigating better alternatives of Bazett's correction to be more appropriate for interventional studies can be another recommendation for future research.

CONCLUSION

Risperidone may have significant effects on Q-T interval and Q-T dispersion. Physicians and psychiatrists should be aware that a prolonged QTc interval is a potential indicator of cardiovascular risk and should be cautious in prescribing potentially QT-prolonging medications at least to certain patients. Before prescribing antipsychotics that may increase the QTc interval, the clinician should ask about family and personal history of sudden cardiac death, presyncope, syncope and cardiac arrhythmias and recommend cardiology consultation if history is positive.

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