Schizophrenia Research 179 (2017) 70–74

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

QTc interval lengthening in first-episode schizophrenia (FES) patients in the earliest stages of antipsychotic treatment

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ARTICLE INFO

Article history:
Received 19 April 2016
Received in revised form 20 September 2016
Accepted 1 October 2016
Available online 7 October 2016

Keywords:
QTc interval
Antipsychotics
First-episode schizophrenia
Short-term

ABSTRACT

Antipsychotic use is reported to be associated with a higher risk of sudden cardiac death and new users are especially susceptible to that risk. In this study, we focused on the ability of antipsychotics to prolong the QTc interval at the earliest stages of antipsychotic use. We employed a retrospective cohort study design in a naturalistic setting where having three ECG measurements over time (at baseline and after drug exposure) in antipsychotic-naïve, first-episode schizophrenia (FES) inpatients. The results revealed, in this relatively homogeneous, drug naïve FES patient sample, that QTc intervals were statistically significantly prolongated after a relatively short term (2–4 weeks) of antipsychotic treatments, compared with baseline. After about 2 or 4 weeks of antipsychotic use, the risk of abnormal QTc prolongation was higher than at baseline. These results reinforce the importance of monitoring risk factors and assessing QTc prolongation at the beginning and throughout treatment with antipsychotics.

1. Introduction

The QT interval refers to the time between the start of the QRS complex and the end of the T wave on an electrocardiogram (ECG). This interval reflects the time span of ventricular depolarization and repolarization. Prolongation of the rate-corrected QT interval (QTc) is considered an ECG marker of arrhythmogenic potential; long QTc is associated with torsade de pointes and sudden cardiac death (Wenzel-Seifert et al., 2011).

Reports of high risk of sudden death in those taking antipsychotics (Haddad and Anderson, 2002; Ray et al., 2001; Straus et al., 2004; Wenzel-Seifert et al., 2011) have increased concern about the ability of antipsychotics to prolong the QTc interval and cause torsades de pointes and other cardiac arrhythmias (Reilly et al., 2000; van Noord et al., 2009). In the past decades, many studies in different settings have assessed QT interval prolongation and sudden death in psychotropic drug therapy. Most of the studies involved chronic schizophrenia patients with long-term antipsychotic use (Haddad and Anderson, 2002; Nose et al., 2015; Ozeki et al., 2010; Ramos-Rios et al., 2010; Ray et al., 2001; Reilly et al., 2000; Straus et al., 2004; van Noord et al., 2009; Wenzel-Seifert et al., 2011; Yang et al., 2011; Zarate and Patel, 2001). There are few studies which explored whether antipsychotic drugs are associated with QTc prolongation in patients who were drug-naïve at baseline. And these studies were largely limited to controlled clinical trials and/or small samples(Agelink et al., 2001; Blom et al., 2011; Correll et al., 2011; Czekalla et al., 2001; Harrigan et al., 2004; Muscatello et al., 2014; Potkin et al., 2013; Rettenbacher et al., 2005; Sala et al., 2005; Suzuki et al., 2013; Yerrabolu et al., 2000). Few studies have explored whether antipsychotic drugs are associated with QTc prolongation in first-episode schizophrenia (FES) patients at the earliest stages of drug exposure.

There are several reasons why antipsychotics-naïve FES patients may be of particular interest regarding QTc prolongation. First, second, in chronic schizophrenia patients with long-term antipsychotics use, some cases of QTc prolongation and cardiovascular death may be secondary to increased metabolic risk in those patients (Haddad and Anderson, 2002; Ramos-Rios et al., 2010; Ray et al., 2001; Reilly et al., 2000; Straus et al., 2004; van Noord et al., 2009; Wenzel-Seifert et al., 2011; Zarate and Patel, 2001). Third, chronic schizophrenia patients

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http://dx.doi.org/10.1016/j.schres.2016.10.006
0920-9964/

may have other factors for QTc prolongation (Wenzel-Seifert et al., 2011) including comorbid cardiovascular disease (Vieweg, 2002), other somatic disease, abnormal glucose metabolism (Shin et al., 2005), administration of pro-arrhythmic medications and antidepressants (particularly tricyclic antidepressants [TCAs]) (Sala et al., 2005), long-lasting low parasympathetic tone or other effects of mental illness which may be confounding factors (Bär et al., 2005; Chang et al., 2013; Wenzel-Seifert et al., 2011).

Last but not least, in current users of antipsychotics, there is a relationship between risk of sudden death and antipsychotic use (Ray et al., 2009). In that study, current use of antipsychotics was reported to be associated with a 1.59–2.86 fold increase in risk of sudden cardiac death (Ray et al., 2009), and short-term (≤90 days) antipsychotic users seem to be at the highest risk (Straus et al., 2004). Those reasons raised the particular attention paid to the ability of antipsychotics to prolong QTc in FES patients at the earliest stages of antipsychotics use.

Here, we conducted a retrospective cohort study in a naturalistic setting, in which patients were antipsychotics-naïve and had FES. Three ECG measurements were available over 30 days (at baseline before the beginning of treatment, after drug treatment of about 2 weeks, and after drug treatment of about 4 weeks. We explored whether antipsychotropic drugs were associated with QTc prolongation.

2. Methods

2.1. First-episode schizophrenia cases

The retrospective cohort **s**tudy was approved by the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University. The clinical practice and Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University were based on the Helsinki declaration. Guardians of patients had reviewed and signed a written informed consent upon admission, which allow researchers get access to patients' record and conduct research activities by use of the related data.

Patients with an ICD-10 diagnosis of FES and never previously treated with antipsychotics or other psychotropic drugs were included. These FES cases, studied between October 2008 and October 2015, were from the Second Affiliated Hospital of Xinxiang Medical University.

Patients with arrhythmia disturbances of cardiac rate and rhythm, atrial fibrillation or bundle-branch block, pre-existing cardiac diseases, history of prolonged QTc, family history of sudden death, alterations of hepatic or renal function, and history of alcohol or other substance dependence were excluded. Patients taking β-blockers other than for the treatment of akathisia were also excluded.

First-episode patients who had ECG measurements over time (baseline: before the beginning of treatment, second measurement: about 2 weeks with drug treatment, and third measurement: with about 4 weeks of drug treatment) were collected to analyze the association between antipsychotic drugs and QTc intervals in the FES patients at the earliest stage of antipsychotic use.

2.2. Data collection and analysis

Demographic details including age, gender, and race were obtained. Current tobacco and alcohol use and family history of cardiovascular diseases was recorded. Information regarding psychiatric diagnosis, medication, dosage, heart rate, QT interval duration was recorded and confirmed by cardiologists.

12-Lead ECGs at 50 mm/s were obtained using an electrocardiography machine with automatic analysis function. The QT interval was measured from the start of the QRS complex to the end of the T wave. To adjust for heart rate, mean QT intervals of the entire ECG were calculated by Fridericia [QtcFrid = QT (heart rate/60)$^{1/3}$] (Fridericia, 1920) and Framingham formula [QTcFram = QT + 154 (1–60/heart rate)] (Sagie et al., 1992), respectively, to confirm the data. QTcfram denoted Framingham heart rate corrected QT, QTcfrid denoted Fridericia's heart rate corrected QT.

2.3. Statistical analysis

Continuous data were used to compare the difference between baseline and treatment conditions, using paired *t*-test or repeated measures ANOVA as appropriate. For categorical data, we used Chi-square analysis to calculate the relative risk between baseline and after use of antipsychotics. We analyzed the potential risk factors (gender, age and mono-combined therapy) by univariate regression and multivariate stepwise regression. Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 17.0). Statistical significance was defined as $p < 0.05$.

3. Results

A flow-chat of cases included were show in Fig. 1.

3.1. Demographic and treatment characteristics

A total of 393 FES patients who had an electrocardiogram record before drug therapy (ECG1) and at least once repeated measure of ECG record during inhospital were enrolled in the study (168[42.7%] men, 225[57.3%] women; mean age 25.3 years, range:10–62). 365 (92.9%) patients were younger than 40 years. 369 patients had a second electrocardiogram record at about 2 weeks of drug treatment (ECG2), 335 patients had a third electrocardiogram record at about 4 weeks of drug treatment (ECG3). Overall, 303 patients had all three electrocardiogram records.

The mean illness duration was 5.1 (SD 6.6) months. Among all inpatients, 195 cases (49.6%) had multi-drug therapy, 198 cases (50.3%) had mono-drug therapy, of which 92.1% were the second generation antipsychotics. Adjunctive medications consisted mainly of antipsychotics (37.8%), antidepressants (8.1%) and mood stabilizers (22.7%). The treatment characteristics were summarized in Table 1.

3.2. Antipsychotic drugs and QTc prolongation

Both of the Fridericia and Framingham algorithms generated similar results. The results of Qtcfrid were shown in the supplemental tables.

In general, there were statistically significant ($p = 0.042$, repeated measures ANOVA) differences among the three QTc measures in ECG records. Compared with baseline, QTc was statistically significantly prolonged in QTc2 and QTc3 (Framingham formula, $p = 0.001$, $p =$

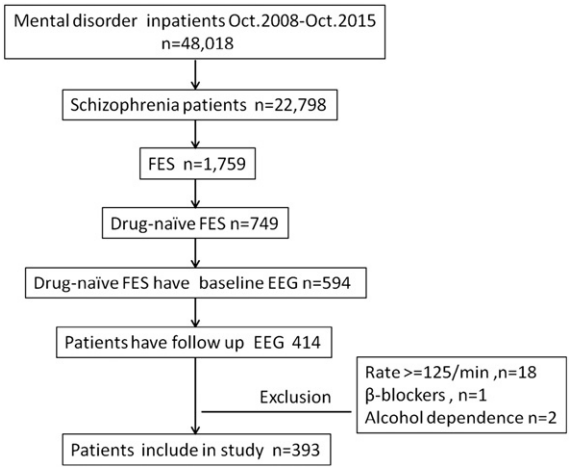

Fig. 1. A flow-chat of cases recruitment.