QTc interval and its variability in patients with schizophrenia and healthy subjects: implications for a thorough QT study

Pooja Hingorani1, Dilip R. Karnad1,2, Mili Natekar1, Snehal Kothari1, Dhiraj Narula1 and Yash Lokhandwala1,3

1 Research Section, Quintiles Cardiac Safety Services, Mumbai, India
2 Seven Hills Hospital, Mumbai, India
3 Arrhythmia Associates, Mumbai, India

Abstract

We compared heart rate-corrected QT interval (QTc) and its within- and between-subject variability, in ECGs recorded several days apart for 207 patients with schizophrenia (age range 19–60 yr) with age- and gender-matched healthy controls. Patients had higher heart rates (mean ± S.D.) than controls [75 ± 15 beats per minute (bpm) vs. 63 ± 10 bpm; p < 0.0001]. QTc by Bazett’s formula (QTcB) overestimated QTc interval at high heart rates; consequently QTcB was longer in patients (412 ± 24 ms) than in controls (404 ± 24 ms; p = 0.0003). QTc by Fridericia’s method (QTcF), which was not influenced by heart rate, was comparable (398 ± 22 ms in patients vs. 401 ± 19 ms in controls; p = 0.17). Between-subject variability in QTcF was similar in patients (17 ms) and controls (16.2 ms) but within-subject variability was larger (13.1 ms vs. 10 ms, respectively). Thus, a larger sample size is required when thorough QTc studies with a cross-over design are performed in patients with schizophrenia than in healthy subjects; sample size is not increased for studies with a parallel design. Last, QTcF is preferred over QTcB in schizophrenia patients with higher heart rates.

Received 23 August 2011; Reviewed 1 December 2011; Revised 21 December 2011; Accepted 2 January 2012; First published online 8 February 2012

Key words: Antipsychotic drugs, cardiac repolarization, electrocardiography, heart rate, within-subject variability.

Introduction

Patients with schizophrenia have higher risk of cardiovascular mortality than the healthy population (Hennekens et al. 2005). Besides coronary artery disease, drug abuse, cigarette smoking, hypercholesterolaemia, hypertension, obesity and diabetes mellitus which are more common in patients with schizophrenia (Bär et al. 2007; Glassman & Bigger, 2001; Hennekens et al. 2005), recent articles have highlighted the association between prolonged QT interval on the ECG and increased risk of sudden death in patients with schizophrenia (Glassman & Bigger, 2001; Nielsen et al. 2011). QT prolongation is a non-invasive biomarker of abnormal cardiac repolarization. When cardiac repolarization is lengthened beyond the normal limits and its duration varies in different regions of the ventricular myocardium, it predisposes to potentially fatal ventricular arrhythmias like torsades de pointes (polymorphic ventricular tachycardia) and ventricular fibrillation (Glassman & Bigger, 2001).

Several commonly used antipsychotic medications alter cardiac repolarization and prolong the QT interval on ECG especially when used in high doses or combinations (CSISG, 2002; Glassman & Bigger, 2001; Nielsen et al. 2011). The QT interval may also be prolonged by autonomic changes, widened QRS complex in the ECG or electrolyte disturbances which are seen during acute psychotic episodes (Bär et al. 2007; CSISG, 2002). However, some important questions about the QTc interval (QT interval corrected for the effect of heart rate) in patients with schizophrenia remain unanswered. Is the QTc interval prolonged...
patients with chronic stable schizophrenia? Is the between-subject variability in QTc interval in schizophrenia greater than in healthy subjects? Is the physiological day-to-day variation in QT interval in these patients different from that in healthy subjects? Since we found very few studies addressing these questions, we retrospectively analysed QT intervals and QT variability in digital 12-lead ECGs recorded in stable medicated patients with schizophrenia participating in several phase 2 and phase 3 clinical trials in this case-control study.

Subjects and methods

Patients with schizophrenia

ECG data from patients with schizophrenia participating in three phase 2 and three phase 3 studies with similar inclusion and exclusion criteria and where Quintiles Cardiac Safety Services, Mumbai, India was the central ECG laboratory were pooled. All studies were approved by respective institutional review boards. Subjects aged between 18 and 65 yr with a primary diagnosis of schizophrenia according to DSM-IV-TR criteria, who were able to comprehend and communicate with study personnel and had signed the study consent form were included. Stable patients were defined as subjects who did not have severe psychosis, acute exacerbation, suicidal ideation or violent behaviour, and had not been hospitalized for exacerbation of schizophrenia or received electroconvulsive therapy in the 3 months prior to study enrolment. Patients with alcohol addiction or drug abuse were also excluded. Patients were allowed to take only one of the following atypical antipsychotic medications: olanzapine, risperidone, quetiapine, ziprasidone or aripiprazole, in the 8 wk prior to baseline.

In order to obtain two ECGs from each patient recorded in the absence of any medication other than those mentioned above, ECGs recorded at the screening visit and at the baseline visit (prior to administration of study medication) were included. Thus, patients were receiving only a single permitted atypical antipsychotic drug when the two ECGs were recorded.

Healthy controls

From seven phase 1 studies, 207 age- and gender-matched healthy subjects were randomly selected as controls by a computer using the PROC SURVEY SELECT function in the SAS statistical software package (SAS Institute Inc., USA). Only subjects who received placebo were included in this analysis because two drug-free ECGs recorded several days apart were required to assess variability in QT interval. All subjects had been screened to exclude cardiovascular disorders including familial long QT syndrome. Use of tobacco or nicotine products in the 6-month period preceding the screening visit was prohibited. Individuals with body mass index (BMI) < 18 or >30 kg/m², a clinically significant abnormality at the screening medical assessment (history, physical examination, clinical laboratory tests, or ECG), or history of drug or alcohol abuse were excluded. Female subjects were included only if they were not pregnant or lactating. All subjects had consented to participate in the individual studies which were approved by the institutional review boards. In all subjects, the first ECG was recorded at the baseline visit. A second drug-free ECG recorded several days later was selected to match the interval between the two ECGs in patients with schizophrenia.

ECGs

ECGs were recorded only in the morning, using high-resolution digital electrocardiographs (Model Eli 250, Mortara Instrument Inc., USA or Model MAC5000, GE Medical Systems, Germany). ECG analysis and measurement of intervals were performed manually in the central ECG laboratory using on-screen digital calipers (CalECG version 1.3, AMPS LLC, USA). Intervals were measured on five consecutive beats in a single lead (lead II) and the average of RR and QT intervals in each ECG were calculated. The RR interval was measured from the peak of the R wave previous complex to the peak of R wave in the complex in which QT is measured. Patients with alcohol addiction or drug abuse were also excluded. Patients were allowed to take only one of the following atypical antipsychotic medications: olanzapine, risperidone, quetiapine, ziprasidone or aripiprazole, in the 8 wk prior to baseline.

In order to obtain two ECGs from each patient recorded in the absence of any medication other than those mentioned above, ECGs recorded at the screening visit and at the baseline visit (prior to administration of study medication) were included. Thus, patients were receiving only a single permitted atypical antipsychotic drug when the two ECGs were recorded.

Statistical analysis

Statistical analysis was performed using SAS version 8.02 (SAS Institute Inc.). Heart rate and QTc interval in the first set of ECGs were compared between the two groups using two-sample t tests. Repeated-measures ANOVA was used to estimate between- and within-subject variability for QTcB and QTcF intervals in patients with schizophrenia and healthy controls. Results are expressed as mean ± S.D.

Results

In this case-control study, we compared ECG parameters in two ECGs recorded an average of 15 d
(range 1–50 d) apart, in 207 patients with schizophrenia (63 females, 144 males) and 207 matched healthy controls (63 females, 144 males). The groups were well matched for age (36 ± 11 yr), gender and interval between the two ECGs.

The mean heart rate in patients with schizophrenia [75 ± 15 beats per minute (bpm)] was 12 bpm higher ($p < 0.001$) than that in healthy subjects (63 ± 10 bpm). The QTcB interval was significantly longer in patients with schizophrenia (412 ± 24 ms; $p = 0.003$) compared to healthy volunteers (404 ± 24 ms), while QTcF interval measurements did not differ significantly (398 ± 22 vs. 401 ± 19 ms; $p = 0.17$). One healthy subject and four patients with schizophrenia (three males, one female) had QTc prolongation with QTcF values between 450 and 480 ms and none had a QTcF interval >480 ms.

On plotting the values of QT, QTcB and QTcF intervals from each ECG against the corresponding heart rate, the QT interval showed an inverse correlation with heart rate (slope $-1.82$, $R^2 = 0.61$, $p < 0.001$) indicating that the QT interval shortened progressively with increasing heart rate. The slope of QTcB interval was significantly positive (slope 0.86, $R^2 = 0.003$, $p < 0.001$), suggesting that QTcB increased progressively with increasing heart rate. The slope of the regression line of QTcF interval vs. heart rate was close to zero (slope $-0.08$, $R^2 = 0.23$, $p = 0.11$), indicating that Fridericia’s correction formula corrected better for the effect of heart rate on the QT interval as it was not significantly influenced by the heart rate. QTcB, Bazett’s formula for QTc, QTcF, Fridericia’s formula for QTc.

We found that the between-subject variability was similar in patients with schizophrenia and healthy controls (Table 1). However, within-subject variability for QTcF and QTcB was lower in healthy controls. Similar results were observed when subgroup analysis was performed based on the interval between the two ECGs.

**Discussion**

We studied resting 12-lead ECGs recorded in medicated patients with schizophrenia in a stable phase and found that patients had a higher heart rate than age- and sex- matched normal healthy controls. Previous studies too have found that patients with schizophrenia have increased heart rates (Bär et al. 2005) which persist even in sleep and after antipsychotic medications (Addis et al. 2003). This has been attributed to decreased parasympathetic vagal output (Toichi et al. 1999), decreased baroreceptor sensitivity and increased sympathetic activity...
(Bär et al. 2007), probably due to disturbance in cortical-subcortical circuits that modulate autonomic function (Valkonen-Korhonen et al. 2003). Physical deconditioning and concomitant medications may also contribute to the higher heart rate (Vancampfort et al. 2011).

Some antipsychotic drugs prolong the QTc interval (Reilly et al. 2000). Hypokalaemia, hypomagnesaemia and hypocalcaemia which are often found during acute psychotic episodes (Lam et al. 2009) and autonomic changes like sympathetic overactivity and decreased vagal tone during agitation, may also affect cardiac repolarization in patients with schizophrenia (Bär et al. 2007; Magnano et al. 2002). Thus, the baseline QTc interval in patients with schizophrenia depends on the interplay between these factors (Alexander et al. 1979; Rettenbacher et al. 2005). We found that the baseline QTcF interval in patients with stable schizophrenia was similar to that in healthy subjects. Our results are similar to those found by Rettenbacher et al. (2005) in a smaller study where the QTc interval in 63 drug-free patients with schizophrenia after a washout period of 1 wk was comparable to that in 31 healthy controls.

The QT interval decreases as heart rate increases and Bazett’s and Fridericia’s methods (Salvi et al. 2010) are commonly used to obtain the heart rate-corrected QT interval (QTc). Many previous authors have found that Bazett’s method overcorrects for the effect of heart rate and may give artificially high values of QTc at higher heart rates (Nielsen et al. 2011; Salvi et al. 2010). It is therefore not surprising that the mean QTcB interval was 8 ms (p = 0.0003) longer in our patients with schizophrenia whose heart rates were on an average 12 beats higher than healthy controls. However, on using Fridericia’s method, which was a better correction method for heart rate in our patients, the QTcF interval did not differ in the two groups. Thus, the method for QT correction must be carefully selected in patients with schizophrenia who are likely to have high resting heart rates.

The QTc interval may vary by as much as 80 ms over a period of days or weeks in healthy persons (Morganroth et al. 1991). Some authors suggest that this diurnal and day-to-day variation may be increased in schizophrenia (Rettenbacher et al. 2005). In order to control for these variables, all ECGs in the present study were recorded in the morning hours, and the ECGs from healthy controls were selected to match the time interval (days) between the two ECGs in the schizophrenia group. We found that the between-subject variability for QTcF and QTcB was comparable in the two groups. However, the within-subject variability in QTc was 3–6 ms greater in patients with schizophrenia than in healthy subjects. This difference persisted regardless of the interval between the two ECGs over a range of 1–50 d. In the only other similar study, Rettenbacher et al. (2005) found that the within- and between-subject variability in schizophrenia and in healthy controls was comparable. However, the number of subjects in their study was small compared to the present study; consequently their estimates of variability were wider than ours and it is not surprising that they found no

<table>
<thead>
<tr>
<th>QTc</th>
<th>Group</th>
<th>No. of subjects</th>
<th>Between (ms)</th>
<th>Within (ms)</th>
<th>No. of subjects</th>
<th>Between (ms)</th>
<th>Within (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF</td>
<td>All subjects</td>
<td>202*</td>
<td>17.0</td>
<td>13.1</td>
<td>207</td>
<td>16.2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>≤ 5 d</td>
<td>89</td>
<td>18.6</td>
<td>13.7</td>
<td>90</td>
<td>18.0</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>6–10 d</td>
<td>13</td>
<td>14.7</td>
<td>12.2</td>
<td>14</td>
<td>14.3</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>11–15 d</td>
<td>19</td>
<td>19.4</td>
<td>11.8</td>
<td>19</td>
<td>13.5</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>&gt; 15 d</td>
<td>81</td>
<td>15.0</td>
<td>13.0</td>
<td>84</td>
<td>14.5</td>
<td>10.3</td>
</tr>
<tr>
<td>QTcB</td>
<td>All subjects</td>
<td>202*</td>
<td>18.0</td>
<td>15.7</td>
<td>207</td>
<td>19.7</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>≤ 5 d</td>
<td>89</td>
<td>20.7</td>
<td>15.5</td>
<td>90</td>
<td>22.1</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>6–10 d</td>
<td>13</td>
<td>21.2</td>
<td>13.4</td>
<td>14</td>
<td>15.1</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>11–15 d</td>
<td>19</td>
<td>15.2</td>
<td>16.4</td>
<td>19</td>
<td>16.2</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>&gt; 15 d</td>
<td>81</td>
<td>13.7</td>
<td>16.1</td>
<td>84</td>
<td>17.0</td>
<td>12.8</td>
</tr>
</tbody>
</table>

QTc, Heart rate-corrected QT interval; QTcB, Bazett’s formula for QTc; QTcF, Fridericia’s formula for QTc.
* Five patients in whom the QT interval was measured in different ECG leads in the second ECG were excluded from this analysis.
difference in within- and between-subject variability in the two groups. In a recent thorough QT study which assessed the effect of asenapine on the QT interval in patients with schizophrenia (Chapel et al. 2009), the between-subject variability was 15.3 ms which is similar to the value of 17 ms observed in our study.

It must be noted that the within-subject variability in the present study pertains to changes in QTc intervals over a period of days or weeks (Bexton et al. 1986), and should not be confused with beat-to-beat QT variability which assesses variability in QTc interval in a series of consecutive beats recorded over a relatively shorter period of hours or minutes (Bär et al. 2007; Jindal et al. 2009). Beat-to-beat QT variability analysis is used to study the effects of autonomic influences on cardiac repolarization using complex mathematical and computational methods (Bär et al. 2007; Jindal et al. 2009) and decreased beat-to-beat variability has been associated with increased risk of cardiac arrhythmias and sudden death in a variety of cardiac conditions (Berger et al. 1997; Myredal et al. 2008). Recent studies have shown reduced beat-to-beat variability in schizophrenia too, but its clinical significance is not clear and longitudinal studies associating these abnormalities with cardiac events are awaited (Bär et al. 2007; Jindal et al. 2009).

Limitation and strengths
Although it would be ideal to compare drug-free ECGs from patients with schizophrenia with healthy subjects, ECGs in the present study were not recorded during a drug-free period as this is logistically and ethically difficult. One could discontinue antipsychotic drugs for a few weeks in patients with mild schizophrenia to study variability in the QTc interval. However, the changes in QTc in these patients would be small, and a very large sample would be required to detect any difference. Conversely, the difference is likely to be more pronounced in moderate or severe disease, but it would be unethical to discontinue antipsychotic drugs for several weeks in these patients. However, while some antipsychotic drugs like haloperidol, droperidol, chlorpromazine, sulthiapine, sertindole and thioridazine prolong the QTc interval, most atypical antipsychotic agents that our patients were permitted, do not affect the QTc interval (Alvarez & Pahissa, 2010; Bär et al. 2007; Reilly et al. 2000; Sala et al. 2005; Titier et al. 2005). Moreover, patients in our study received only a single atypical antipsychotic drug; this is important since polypharmacy is a proven risk factor for drug-induced QTc prolongation (CSISG, 2002; Sala et al. 2005). On the other hand, use of digital electrocardiographs, analysis of ECGs in a central ECG laboratory using highly standardized techniques by trained readers, inclusion of a large number of patients, and use of age- and gender-matched controls are some of the strengths of the present study.

Conclusions
Our study showed that patients with schizophrenia in a stable phase had higher heart rates than healthy controls, but the QTc interval was not prolonged. We also found that the commonly used Bazett’s correction formula overestimates QTc at higher heart rates and should not be used in patients with schizophrenia; Fridericia’s correction method is preferred. The between-subject variability in the QTc interval was similar in patients with schizophrenia and in healthy subjects, but within-subject variability in patients is higher than in healthy controls.

Within- and between-subject variability are important in planning studies; a larger sample size is required if the variability is large (Salvi et al. 2010). Our results suggest that if a parallel study design is used to assess effects of a new antipsychotic drug on cardiac repolarization (thorough QT/QTc study), the sample size remains the same regardless of whether the study is performed in healthy volunteers or in patients with schizophrenia. However, for a cross-over study design (Julious, 2004), a significantly larger sample size will be required for a study to be performed in patients with schizophrenia who have greater within-subject variability.

Acknowledgements
None.

Statement of Interest
Pooja Hingorani, Mili Natekar, and Snehal Kothari are employees of Quintiles Cardiac Safety Services, Mumbai. Dilip Karnad, Dhiraj Narula and Yash Lokhandwala are consultants to Quintiles Cardiac Safety Services, Mumbai.

References
Alexander PE, Van Kammen DP, Bunney Jr. WE (1979). Serum calcium and magnesium levels in schizophrenia ii.
possible relationship to extrapyramidal symptoms. 
*Archives of General Psychiatry* **36**, 1372–1377.


