QTc Interval Measurement and Metabolic Parameters in Psychiatric Patients Taking Typical or Atypical Antipsychotic Drugs: A Preliminary Study

Paul Mackin, M.B., B.S., Ph.D., M.R.C.Psych., and
Allan H. Young, M.B., Ch.B., Ph.D., F.R.C.Psych.

Background: Antipsychotic drugs have been associated with prolongation of the QTc interval on the electrocardiogram, and QTc prolongation is, in turn, associated with an increased risk of cardiac arrhythmias and sudden death. Antipsychotic polypharmacy has been implicated in reduced survival, possibly secondary to cardiotoxic effects of antipsychotic medication. Abnormalities of glucose homeostasis, which may be more common in individuals with major mood disorders and schizophrenia, also affect the QTc interval.

Method: We performed detailed assessment of metabolic parameters in 103 psychiatric outpatients, from across the diagnostic spectrum, who had been taking antipsychotic medication (typical, atypical, or a combination thereof) for a minimum of 6 months. We measured the QTc interval in a subset of these patients (N = 65).

Results: Only 2 patients (3%) had a prolonged QTc interval. There was a statistical trend (p = .08) toward a lower QTc interval in patients receiving antipsychotic polypharmacy. QTc interval was associated with age (p = .04) but not with any metabolic parameter.

Conclusion: QTc prolongation in this population is uncommon. There was a significant association between increasing age and QTc interval, but cardiac repolarization was not related to any metabolic parameter. Further large prospective studies of similar patients are needed to confirm these findings.

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Received Jan. 13, 2005; accepted April 20, 2005. *From the School of Neurology, Neurobiology, and Psychiatry, University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom.*

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Corresponding author and reprints: Paul Mackin, Ph.D., School of Neurology, Neurobiology, and Psychiatry, University of Newcastle upon Tyne, Leazes Wing, Royal Victoria Infirmary, Queen Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, United Kingdom (e-mail: paul.mackin@ncl.ac.uk).

The QT interval on the electrocardiogram (ECG) represents the period of time from the onset of ventricular depolarization to the completion of ventricular repolarization, and the rate-corrected interval is denoted as QTc. Much attention has been focused on prolongation of the QTc interval because of the association with cardiac arrhythmias, such as torsades de pointes, and sudden death.[1] Many antipsychotic drugs have electrophysiologic effects on the heart similar to that of quinidine,[2] and reports of sudden unexplained death in patients taking antipsychotic drugs[2,3] have raised concerns that antipsychotic-induced arrhythmias may underlie this phenomenon.

A study of 495 psychiatric patients,[4] the majority of whom were taking typical agents, reported that droperidol and thioridazine caused QTc lengthening in a dose-related manner. A further study[5] identified an excess of sudden deaths in patients taking thioridazine. Subsequent to these observations, droperidol was withdrawn from the market, and changes were made to the licensed indications for thioridazine. Other reports have described QTc interval prolongation following treatment with chlorpromazine[6] and haloperidol taken at doses exceeding 20 mg per day.[7] Data regarding the other typical agents are inconclusive, although several studies have reported QTc interval prolongation in patients receiving a variety of typical agents, even at conventional doses.[8,9]

Notwithstanding the concerns regarding the association between antipsychotic medication and QTc interval prolongation, until recently there has been a paucity of meaningful data addressing this apparent association. The advent of increasing regulatory control and postmarketing drug surveillance has resulted in better-quality studies examining the role of antipsychotic drugs, particularly the newer atypical agents, with regard to QTc interval prolongation, cardiac arrhythmias, and sudden death. The currently available data have been recently reviewed by Taylor.[10] Sertindole has a clear association with QTc prolongation,[11] and there appears to be a dose-related effect of risperidone[12] and clozapine[13] on QTc interval. Olanzapine[14] and quetiapine[15] appear not to have significant effects on cardiac electrophysiology in clinical studies, and data for amisulpride are too few to draw any meaningful

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conclusions. In animals, however, there is evidence that haloperidol, clozapine, olanzapine, risperidone, and sertindole cause QT prolongation that is concentration-related.[16]

Antipsychotic polypharmacy may be associated with reduced survival,[17] although the mechanism underlying this observation is unclear. Expert opinion appears to favor the avoidance of antipsychotic polypharmacy because of the potential for additive effects on the QTc interval,[10] although there are few data to support this view.

Quite apart from the deleterious effects of antipsychotic drugs on cardiac electrophysiology, QTc prolongation also appears to be associated with increased mortality in the elderly.[18] Impaired glucose tolerance (IGT) and diabetes[19] as well as fasting insulin levels[20] also correlate with the QTc interval. The relationship between obesity and cardiac repolarization is less clear, as some studies report an association[21,22] while others find no association between QT prolongation and anthropometric parameters.[23]

Obesity and metabolic dysfunction are common in psychiatric patients taking antipsychotic medication,[24] and abnormalities of glucose homeostasis and visceral fat distribution may be more common in severe mental illnesses such as schizophrenia,[25] a population in whom the use of antipsychotic medication is common. There is a clear need, therefore, for studies examining the relationship between QTc interval, antipsychotic use, and metabolic dysfunction. We hypothesized that QTc interval would correlate with measures of obesity as well as fasting glucose and insulin levels, and that psychiatric patients receiving antipsychotic polypharmacy would have a greater incidence of QTc interval prolongation.

METHOD

We randomly recruited 103 patients from psychiatric outpatient clinics in the north of England. Our original study was designed to determine the prevalence of undiagnosed metabolic disease in this population, and the results have been previously reported.[24] Subjects were recruited irrespective of psychiatric diagnosis. The only inclusion criterion was that the individual had been taking prescribed typical or atypical antipsychotic medication or a combination thereof for a minimum of 6 months. For the purposes of this study, "high dose" is defined as > 1000 mg chlorpromazine equivalents per day or doses exceeding the British National Formulary maximum recommended doses. Although changes of drug within the same class (i.e., typical or atypical) during this period of 6 months were permitted, all recruited subjects had been receiving the same antipsychotic drug for a minimum of 6 months. Exclusion criteria were as follows: a known diagnosis of type 1 or type 2 diabetes mellitus, anorexia nervosa, bulimia nervosa, neoplastic disease, or alcohol dependence. After complete description of the study to the subjects, written informed consent was obtained, and the study was approved by the Newcastle upon Tyne Regional Ethics Committee.

Following an overnight fast (subjects were given written instructions to fast from midnight on the evening prior to assessment, but were not observed), venous blood was withdrawn for glucose, glycosylated hemoglobin (HbA_{1c}), insulin, and lipid profile estimation. Insulin was measured by enzyme-linked immunosorbent assay (ELISA). Intra-assay coefficient of variation (CV) was 7.5%, and inter-assay CV was 4.2%. The homeostatic model assessment (HOMA2)[26] was used to assess insulin resistance and is expressed as %S (insulin sensitivity). The model is calibrated to give %S values of 100% in normal young adults when using currently available assays for insulin. Impaired fasting glucose was defined as fasting blood glucose between 6.1 and 7.0 mmol/L, and diabetes mellitus was defined as fasting blood glucose > 7.0 mmol/L or HbA_{1c} > 9%. Metabolic syndrome was defined according to World Health Organization criteria as the presence of insulin resistance (type 2 diabetes mellitus or IGT), plus any 2 of the following: hypertension, elevated plasma triglycerides and/or low high-density lipoprotein (HDL) cholesterol, and elevated body mass index (BMI).[27]

Demographic details were obtained, which included age, gender, and racial origin. Current tobacco, alcohol, and illicit substance use was recorded as well as family history of cardiovascular disease and diabetes mellitus. Information regarding psychiatric diagnosis, duration of illness, number of admissions to psychiatric inpatient facilities, medication (including nonpsychiatric drugs), and dosage was recorded and confirmed, where necessary, by reference to the case notes and prescription charts. In addition, height, weight, and waist and hip circumference were recorded.

From this original cohort, a subset of 65 patients was available to attend for a 12-lead ECG taken at 50 mm/s. This was performed at 10:00 a.m. on the study day using a MAC 1200ST portable ECG machine (GE Medical Systems, Slough, Berkshire, United Kingdom). A digitizer tablet (CalComp 9000, CalComp, Phoenix, Ariz.) was used to analyze 3 complexes from each standard lead of the 12-lead ECG. One of the investigators who was blind to origin of the ECG performed the analysis. The QT interval was defined as the period from the onset of the QRS complex to the end of the T wave, defined as a return to the T-P baseline, or in the presence of U waves, the T-U nadir. When the end of the T wave could not be reliably identified, the lead was excluded from analysis. Mean QT intervals for the 12 leads were corrected for heart rate using Bazett's formula ($QTc = QT / \sqrt{RR\ interval}$) to obtain the QTc mean. Conventional cutoff points were used to define QTc prolongation (men, 450 ms; women, 470 ms).

Table 1. Characteristics of 65 Patients Taking Antipsychotic Drugs

Characteristic	Value
Age, mean (SD), y	45.3 (11.8)
Gender, N (%)	
Male	31 (48)
Female	34 (52)
Ethnicity, white, N (%)	65 (100)
Duration of illness, mean (SD), mo	215.8 (150.7)
No. of admissions, mean (SD)	5.7 (5.5)
Alcohol units per wk, mean (SD)	6.6 (10.5)
Smoker, N (%)	30 (46.2)
Cigarettes per d, mean (SD)	14.9 (18.1)
Family history, N (%)	
Diabetes mellitus	18 (27.7)
Cardiovascular disease	35 (53.8)
BMI, mean (SD), kg/m^2	29.1 (5.1)
Waist-to-hip ratio, mean (SD)	0.87 (0.09)
HbA_{1c}, mean (SD), %	5.2 (0.5)
Blood glucose, mean (SD), mmol/L	5.2 (0.9)
Serum insulin, mean (SD), μIU/mL	12.8 (15.4)
%S, mean (SD)[a]	102.6 (60.4)
Cholesterol, mean (SD), mmol/L	5.6 (1.1)
Triglycerides, median (range), mmol/L	2.1 (0.6–8.4)
HDL, mean (SD), mmol/L	1.4 (0.4)
LDL, mean (SD), mmol/L	3.4 (0.9)
QTc, mean (SD), ms	413.8 (23.8)
Impaired fasting glucose, N (%)	8 (12.3)
Metabolic syndrome, N (%)	3 (5)
Antipsychotic monotherapy, N (%)	
Typical	13 (20.0)
Atypical	40 (61.5)
Antipsychotic polypharmacy, N (%)	12 (18.5)
High-dose antipsychotic, N (%)	8 (12.3)

[a]Assessed by the HOMA2 method.[26]
Abbreviations: BMI = body mass index, HbA_{1c} = glycosylated hemoglobin, HDL = high-density lipoprotein, HOMA2 = homeostatic model assessment, LDL = low-density lipoprotein, %S = insulin sensitivity.

Table 2. Doses of Antipsychotic Drugs Taken by Psychiatric Outpatients (N = 65)

	Dose	
Antipsychotic Drug	Mean (SD)	Range
Typical		
Chlorpromazine	116.6 (72.2) mg/d	75–200 mg
Zuclopenthixol[a]	700 mg/2 wk[b]	…
Flupenthixol[a]	81.5 (58.3) mg/2 wk	50–200 mg
Haloperidol[a]	103.0 (37.1) mg/2 wk	25–200 mg
Trifluoperazine	9.5 (7.7) mg/d	4–15 mg
Sulpiride	450.0 (300) mg/d	200–800 mg
Atypical		
Amisulpride	500 (141.4) mg/d	400–600 mg
Clozapine	637.5 (335.1) mg/d	300–950 mg
Olanzapine	15.1 (7.2) mg/d	5–30 mg
Risperidone	6.9 (6.7) mg/d	0.5–20 mg
Quetiapine	344.4 (224.2) mg/d	100–800 mg

[a]Prescribed as depot medication.
[b]One patient only.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 11, SPSS Inc., Chicago, Ill.). Serum triglycerides were not normally distributed, and values were $\log_{10}$ transformed. The difference in QTc value between patients prescribed monotherapy and combination antipsychotic treatment was assessed using the Student t test. Pearson's product moment correlation coefficient (Pearson's r) was used to measure the degree of correlation between QTc and age and various metabolic and anthropometric measures, and logistic regression analysis was used for binary values. Results are expressed as mean ± SD unless otherwise stated, except for nonnormally distributed data (triglycerides), which are expressed as median (range). Statistical significance is defined as $p < .05$.

RESULTS

The prevalence of metabolic disease in the original cohort of 103 patients has already been reported.[24] Details of the subset of 65 patients included in this study are given in Table 1. With regard to diagnosis, patients fell into the following diagnostic categories: bipolar disorder (N = 20, 30.8%), schizophrenia (N = 20, 30.8%), schizoaffective disorder (N = 9, 13.8%), and other mood and anxiety disorders (N = 16, 24.6%). Thirteen patients were taking typical agents, 40 were taking atypical agents, and 12 patients were prescribed combination treatment. Doses of antipsychotic medication are given in Table 2. Doses of antipsychotic drugs were similar across diagnostic groups, with the exception of risperidone, which was prescribed at a significantly higher dose in patients with a diagnosis of schizoaffective disorder (18.0 ± 2.8 mg/day) than in patients in other diagnostic groups (bipolar disorder, 2.3 ± 2.5 mg/day; schizophrenia, 6.0 ± 2.0 mg/day; other, 1.75 ± 0.35 mg/day; $F = 25.9$, $df = 3$, $p = .02$).

Of the 65 patients, 15 (23%) were not prescribed any medication in addition to antipsychotic drugs. Twenty-one (32%), 18 (28%), 7 (11%), and 4 subjects (6%) were taking an additional 1, 2, 3, or 4 drugs, respectively. Data regarding individual additional drugs are given in Table 3.

Two patients (3%; 1 man, 1 woman) had a prolonged QTc interval; 1 of the 2 patients was taking 4 additional drugs and the other was taking 1 additional drug. There was a statistical trend ($p = .08$) toward a lower QTc interval in patients taking antipsychotic polypharmacy (402.6 ± 24.1 ms) compared with patients taking a single antipsychotic agent (416.4 ± 23.2 ms). There was no interaction between the number of additional nonantipsychotic drugs and QTc interval ($F = 1.3$, $df = 4$, $p = .3$). Comparison of QTc interval between patients taking no additional nonantipsychotic medication and those taking additional medication (listed in Table 3) revealed no significant differences for any drug. QTc interval correlated significantly with age ($r = 0.26$, $p = .04$). There was no interaction between QTc interval and gender, diagnostic group, smoking status, family history of diabetes mellitus or cardiovascular disease, high-dose antipsy-

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Table 3. Additional Nonantipsychotic Drugs Taken by Psychiatric Outpatients Prescribed Typical or Atypical Antipsychotic Drugs (N = 65)

Drug	N (%)
SSRI	20 (30.8)
Tricyclic antidepressant	6 (9.2)
Venlafaxine	8 (12.3)
Mirtazapine	5 (7.7)
Lithium	10 (15.4)
Sodium valproate	7 (10.8)
Carbamazepine	1 (1.5)
Lamotrigine	5 (7.7)
Benzodiazepine	22 (33.8)
Procyclidine	12 (18.5)
Thyroxine	3 (4.6)
Bendrofluazide	1 (1.5)
β-Blocker	4 (6.2)

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 4. Correlation Between QTc Interval and Demographic, Anthropometric, and Metabolic Parameters in 65 Patients Taking Antipsychotic Drugs

Characteristic	r	p
Age	0.26	.04
Tobacco consumption	0.13	.32
Alcohol consumption	–0.03	.82
BMI	–0.09	.47
Waist-to-hip ratio	–0.01	.97
HbA_{1c}	0.20	.12
Fasting blood glucose	0.15	.25
Serum insulin	0.09	.45
%S[a]	–0.03	.85
Cholesterol	–0.11	.42
Triglycerides	–0.07	.61
HDL	–0.07	.60
LDL	–0.06	.66

[a]Assessed by the HOMA2 method.[26]
Abbreviations: BMI = body mass index, HbA_{1c} = glycosylated hemoglobin, HDL = high-density lipoprotein, HOMA2 = homeostatic model assessment, LDL = low-density lipoprotein, %S = insulin sensitivity.

chotic medication, or the presence of impaired fasting glucose or the metabolic syndrome. The results of correlation analysis between the various demographic, anthropometric, and metabolic parameters are given in Table 4.

There were no differences with regard to QTc interval between any of the atypical agents ($F = 7.1$, $df = 4$, $p = .58$), although the relatively small numbers in these groups preclude any firm conclusions to be drawn from these data.

DISCUSSION

The potential for cardiovascular toxicity of the older-generation, typical antipsychotic drugs is well established,[4] and although the newer, atypical agents have often been reported to have a more benign side effect profile, their widespread use has highlighted concerns with many of these agents with regard to arrhythmias and QTc interval prolongation.[28] In our study, however, only 2 patients (3%) had a prolonged QTc interval; neither patient was receiving high-dose or multiple antipsychotic drugs. There was a significant correlation between age and QTc interval in this group, although no such association existed between cardiac repolarization and metabolic or anthropometric parameters. There was no association between the number of additional nonantipsychotic drugs and QTc interval, nor was there any interaction between any of the additional nonantipsychotic drugs and QTc interval. The absence of a prolonged QTc interval in patients receiving antipsychotic polypharmacy (and indeed the presence of a statistical trend in the opposite direction, i.e., toward a shorter repolarization period) is an interesting observation.

To our knowledge, this is the first study specifically to explore the relationship between QTc interval and detailed metabolic and anthropometric measures in a cross section of psychiatric patients taking typical and atypical antipsychotic drugs. Our study was designed to investigate the relationship between these parameters in light of the absence of data from this patient population and the conflicting results of studies in other patient groups. The paucity of data addressing the question of the impact of metabolic dysfunction and antipsychotic polypharmacy on cardiac electrophysiology is surprising given the association between antipsychotic use and reduced survival[17,29] together with the emerging data highlighting the prevalence of metabolic disease in patients with severe mental illness.[24,25,30]

The main weakness of this study is the relatively small sample size. Although causal relationships cannot be determined from a cross-sectional study, associations can be identified. The lack of such an association between QTc interval and any parameter except age in this study is an important observation that requires replication in a larger sample size. Given the relatively small number of subjects, however, this study may have lacked the statistical power to identify other significant associations, and these results should, therefore, be considered as preliminary.

Increased mortality has been reported in a study of patients with schizophrenia receiving antipsychotic polypharmacy,[17] although measures of cardiac electrophysiology were not undertaken in this study by Waddington and colleagues. Some authorities have recommended that antipsychotic polypharmacy is avoided as the risk of QTc interval prolongation may be increased,[10] although there are few clinical data to support this assertion. Preclinical data have, however, shown dose-related effects of a number of antipsychotics on cardiac repolarization and arrhythmias,[16] and as such, pending further investigation, assessment of cardiovascular status and ECG monitoring are indicated in patients treated with high-dose or polypharmacy antipsychotic treatment. Our results highlight

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the need for further large, prospective clinical studies investigating the effects of antipsychotic polypharmacy on cardiac repolarization.

Patients with severe mental illness, many of whom will be prescribed antipsychotic medication, are at an increased risk of premature mortality by suicide, homicide, accidents, and other unnatural causes.[31] Patients with severe mental illness are also at a higher risk for cardiovascular[32] and metabolic disease,[25] including diabetes,[33] all of which may be associated with reduced survival independent of antipsychotic use. Establishing the causes of sudden death in these patients is further complicated by the reported association between QTc prolongation and cardiovascular disease, obesity, and metabolic disease such as diabetes mellitus and the metabolic syndrome.[18–23] We did not find an association between any anthropometric or metabolic parameter in this study, which may suggest that the excess mortality observed in these patients is not due to cardiac repolarization abnormalities.

The association between QTc interval lengthening and increasing age is controversial. Some[34,35] but not all[36] studies have reported increasing QTc interval with age. Interestingly, Mangoni and colleagues[34] reported that both age and BMI independently predicted QTc interval in healthy subjects and suggested that ventricular hypertrophy and myocardial action potential prolongation may be a potential mechanism. There is a lack of data examining the impact of age on QTc interval in psychiatric patients taking antipsychotic drugs, and although a significant correlation existed between age and QTc interval in our study, there was no such interaction with BMI. The association between cardiac repolarization and age may be due to a higher prevalence of cardiovascular disease with advancing age, although this remains speculative in the absence of a more detailed assessment of cardiovascular status in our cohort. It should be noted, however, that despite the association with age, only 3% of patients had a prolonged QTc interval, and no QTc interval was > 500 ms.

These preliminary data require replication in larger sample sizes. The impact of metabolic dysregulation on cardiac physiology in this patient group is poorly understood, and the causes of sudden death and reduced survival in patients with mental illness appear to be complex and multifactorial. In order to increase our understanding of the causes of increased mortality in patients with severe mental illness, and to clarify the interplay between psychiatric medication and metabolic factors, future studies should measure cardiac electrophysiology as well as markers of metabolic disease.

Drug names: carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), droperidol (Inapsine and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), procyclidine (Kemadrin), quetiapine (Seroquel), risperidone (Risperdal), trifluoperazine (Stelazine and others), venlafaxine (Effexor).

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