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ORIGINAL PAPER

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The QTc interval and its dispersion in patients receiving two atypical antipsychotics

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Abstract *Objective* Treatment with atypical antipsychotics may prolong the rate-corrected Q–T interval (QTc) on electrocardiogram and increase the risk of dangerous ventricular arrhythmias. Polytherapy with atypical antipsychotics is becoming common, but the effect of this practice on the QTc has not been explored in detail. *Methods* Among 364 adults treated with atypical antipsychotics randomly selected from consecutive admissions to a single hospital, electrocardiograms with measurable Q–T intervals in at least six leads were available for 38 of 49 patients receiving polytherapy with two atypical antipsychotics. Daily chlorpromazine equivalent, QTc duration and QTc dispersion were assessed in this group and in 73 closely matched patients receiving atypical antipsychotic monotherapy. *Results* The daily chlorpromazine equivalent of atypical antipsychotics was significantly greater in the polytherapy group (525.2 vs. 244.7 mg, $P = 0.0003$). Polytherapy and monotherapy patients were similar with regard to QTc duration, QTc dispersion and proportion of patients with gender-adjusted QTc prolongation (7.9% vs. 9.6%). The QTc duration had only a modest correlation with the total antipsychotic dose ($P = 0.064$). The presence of hypokalemia (3.0–3.5 mEq/l) was not associated with longer QTc intervals. *Conclusions* The common practice of polytherapy with two atypical antipsychotics does not seem to lead to significant QTc prolongation compared to monotherapy.

Key words Atypical antipsychotics · repolarization · QT duration · QT dispersion

Introduction

The prevalence of antipsychotic polytherapy ranges from 10 to 40% in large cohorts of patients with schizophrenia and other psychotic disorders [3, 7] and the combined long-term use of two atypical antipsychotics has significantly increased in the past decade [3]. The efficacy of this practice has not been firmly established, but receiving more than one antipsychotic concurrently has been associated with reduced survival due to cardiac events [6, 12]. The relative risk for premature death has been estimated to be 2.5 per increment of one antipsychotic drug [6].

Antipsychotic drugs have a dose-dependent effect on the myocardial repolarization by inhibiting the delayed potassium rectifier current [4]. Prolonged QTc is a risk factor for *torsade de pointes*, an arrhythmia that may progress to ventricular fibrillation, particularly in patients with QTc greater than 500 ms [4]. The risk for *torsade de pointes* is higher in patients with hypokalemia and in those with a difference between the longest and shortest QTc among the EKG leads, called QTc dispersion, of greater than 100 ms [4]. The risk is likely to be higher at the time of admission for inpatient hospitalization, when a substantial number of psychotic patients are hypokalemic [5]. Other risk factors for prolonged QTc and torsade de pointes include congenital long QT syndromes, antiarrhythmic therapies, age, female gender, bradyarrhythmias, acute coronary syndromes, cerebrovascular accidents, and advanced liver and renal disease [11].

The influence of atypical antipsychotic polytherapy on the QTc interval was assessed in a trial of com-

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bined therapy with clozapine and risperidone [14] and in a case-control study of various antipsychotic combinations [9]. These studies found no significant effect of polypharmacy on QTc duration. However, the number of patients (n = 16 and n = 12, respectively) and antipsychotic combinations in these reports were small, the QTc dispersion was not measured, and correlations with antipsychotic dosages and plasma potassium levels were not attempted. We addressed these issues in a larger case-control study investigating patients treated with two-drug combinations of the six atypical antipsychotics approved for use in the United States.

Methods

Setting and patient population

Data required for this study were collected from the records of 364 individuals treated with atypical antipsychotics randomly selected from among 1,420 consecutive patients admitted to a single 230-bed psychiatric hospital from August 1, 2004 to March 31, 2005. ECG's and serum electrolytes were obtained routinely on all patients admitted to the hospital. The Institutional Review Board of the North Shore—Long Island Jewish Health System, approved retrospective chart review.

Selection of polytherapy and monotherapy subjects

Forty-nine (13.5%) of the 364 patients were treated concurrently with two atypical antipsychotics [2]. These patients were matched for sex and antipsychotic drugs with 98 randomly selected patients treated with one atypical antipsychotic, e.g., a polytherapy female patient receiving clozapine and risperidone was matched with one female patient treated with clozapine and one female patient treated with risperidone monotherapy. ECG's with measurable Q–T intervals in at least six leads were available in the records of 38 polytherapy patients and 73 monotherapy control subjects, comprising the final sample.

Measurement of QTc and plasma potassium

All patients had a 12-lead electrocardiogram recorded with the same instrument (ELI 1200, Mortara Instruments, Milwaukee) and plasma potassium measured at the time of admission. The electrocardiograph is programmed to calculate the "machine QTc". Two medical consultants with extensive experience in ECG interpretation measured the Q–T intervals in all leads in which the onset of the QRS complex and the return of T wave to baseline could be clearly seen. These physicians were blinded to the patients' antipsychotic treatment.

The Q–T duration was corrected for heart rate according to the Bazett's formula [4] and averaged for all assessed leads to produce the "manual QTc". Global dispersion was defined as the difference between the longest and shortest individual lead QTc and adjacent dispersion was defined as the largest difference between two adjacent precordial or frontal plane leads [1]. QTc was considered prolonged if greater than 430 ms in males and 450 ms in females [4].

Calculation of the chlorpromazine equivalent

The atypical antipsychotic doses equivalent to 100 mg/day of chlorpromazine were 2 mg for risperidone, 5 mg for olanzapine, 75 mg for quetiapine, 60 mg for ziprasidone, 7.5 mg for aripiprazole and 50 mg for clozapine [13].

Data analyses

Analyses of variance and χ^2 tests were performed with JMP 5.0.1, 1989–2003, SAS Institute Inc. To examine the effect of variables that could potentially confound the relationship of antipsychotic polytherapy with calculated QTc, we also performed one linear regression analysis and one backward stepwise regression analysis. We added the following variables into the initial models: sex, age, total chlorpromazine equivalent, treatment with each of the six second-generation antipsychotics, antipsychotic polypharmacy, cotreatment with tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, antihistamines, beta-adrenergic blockers, calcium channel blockers and other antihypertensive drugs. All tests were two-sided, with $\alpha < 0.05$.

Results

Polytherapy and monotherapy patients were similar regarding age, sex, race, body mass index, potassium level and frequency of hypokalemia. The frequency of schizophrenia was significantly higher among patients receiving antipsychotic polytherapy. Four patients from the monotherapy group were receiving tricyclic antidepressants (i.e., amitriptyline, despiramine, clomipramine and nortrrityline in one patient each). Polytherapy patients were treated with significantly higher chlorpromazine equivalents than monotherapy control subjects (Table 1).

The mean QTc duration and QTc dispersion were similar in the two groups (Table 1) and for patient treated with 13 different combinations of two atypical antipsychotics Table 2). A trend toward statistical significance was observed for the correlation between QTc and daily chlorpromazine equivalent (P = 0.064).

Three polytherapy patients (two males and one female) and six monotherapy control subjects (all males) had prolonged QTc. The three polytherapy patients were treated with olanzapine and quetiapine (two patients) and with olanzapine and clozapine (one patients). The six monotherapy patients were treated with olanzapine (three patients), quetiapine (two patients), and clozapine (one patient). There were no differences in potassium levels between the patients with abnormal and normal QTc duration (3.80 ± 0.31 vs. 3.84 ± 0.45, P = 0.82) and only one patient with abnormal QTc had a low potassium level. One 60-year-old male treated with 400 mg clozapine daily had a "manual QTc" greater than 500 ms, but the "machine QTc" available to the treating psychiatrist was 456 ms and there were no medical complications during his 5-month hospitalization. Two patients had QTc dispersions greater than 100 ms (a 22-year-old female treated with 300 mg of quetiapine daily, and a 24-year-old female treated with 15 mg of olanzapine daily).

In the logistic regression of variables potentially associated with QTc, only age was significantly correlated with calculated QTc (P = 0.042). In the stepwise regression analysis, three variables were

Table 1 Demographic, clinical and electrocardiographic findings of patients treated with atypical antipsychotics

Characteristic	Total ($N = 111$)	Treated with two atypical antipsychotics ($N = 38$)	Treated with one atypical antipsychotic ($N = 73$)
Age (years ± SD)	43.3 ± 15.4	40.9 ± 12.4	44.5 ± 16.7
Male (N, %)	69 (62.2)	25 (65.8)	44 (60.3)
White (N, %)[a]	77 (70.6)	28 (75.7)	49 (68.1)
Smoking	66 (59.5)	25 (65.8)	41 (56.2)
Body Mass Index (Kg/m^2 ± SD)[b]	28.1 ± 5.6	29.3 ± 6.4	27.4 ± 5.2
Primary psychiatric diagnosis			
Schizophrenia (N, %)	62 (55.9)	28 (73.7)	34 (46.6)*
Bipolar disorder (N, %)	24 (21.6)	7 (18.4)	17 (23.3)
Major depression (N, %)	16 (14.4)	2 (5.3)	14 (19.2)
Substance use disorder (N, %)	5 (4.5)	0 (0.0)	5 (6.8)
Other (N, %)	3 (2.7)	0 (0.0)	3 (4.1)
Second-generation antipsychotics (N, %)			
Olanzapine	36 (32.4)	18 (47.4)	18 (24.7)
Quetiapine	37 (33.3)	19 (50.0)	18 (24.7)
Risperidone	30 (27.0)	16 (42.1)	14 (19.2)
Clozapine	13 (11.7)	7 (18.4)	6 (8.2)
Ziprasidone	16 (14.4)	8 (21.0)	8 (11.0)
Aripiprazole	17 (15.3)	8 (21.0)	9 (12.3)
Second-generation antipsychotic dose (mg/day ± SD)			
Olanzapine	11.5 ± 6.9 (range: 2.5–30)	10.8 ± 65 (range: 5–30)	12.1 ± 7.3 (range: 2.5–30)
Quetiapine	223.3 ± 240.5 (range: 25–900)	231.6 ± 208.8 (range: 25–800)	214.6 ± 270.0 (range: 25–900)
Risperidone	2.1 ± 1.5 (range: 0.5–6)	2.1 ± 1.4 (range: 0.5–6)	2.1 ± 1.6 (range: 1–6)
Clozapine	380.8 ± 262.9 (range: 50–900)	417.9 ± 325.5 (range: 100–900)	337.5 ± 157.9 (range: 50–500)
Ziprasidone	71.2 ± 47.0 (range: 20–180)	67.5 ± 14.9 (range: 40–80)	75.0 ± 64.8 (range: 20–180)
Aripiprazole	16.5 ± 8.8 (range: 5–30)	17.5 ± 8.0 (range: 10–30)	15.6 ± 9.5 (range: 5–30)
Total chlorpromazine equivalent	340.8 ± 372.8 (range: 33.3–2200)	525.2 ± 526.1 (range: 116.7–2200)	244.7 ± 261.1** (range: 33.3–1100)
Non-antipsychotic Treatment			
Anxiolytics/hypnotics (N, %)	58 (52.2)	21 (55.4)	37(50.7)
Antidepressants (N, %)	50 (44.9)	13 (34.2)	37 (50.7)
Tricyclic antidepressants (N, %)	4 (3.6)	0 (0.0)	4 (5.5)
Antihistamines (N, %)	5 (4.5)	1 (2.6)	4 (5.5)
Mood stabilizers (N, %)	38 (34.2)	15 (39.5)	23 (31.5)
QTc (ms ± SD)			
Machine QTc	402 ± 25	400 ± 28	403 ± 22
Calculated QTc	406 ± 28	403 ± 25	408 ± 30
Calculated QTc global dispersion	48 ± 24	52 ± 24	46 ± 24
Calculated QTc adjacent dispersion	40 ± 19	44 ± 20	37 ± 19
Prolonged QTc (N,%)	10 (9.0)	3 (7.9)	7 (9.6)
QTc duration >500 ms (N,%)	1 (0.9)	0 (0)	1 (1.4)
QTc global dispersion >100 ms (N,%)	2 (1.8)	0 (0)	2 (2.7)
Potassium level (mEq/l)[c]	3.8 ± 0.4	3.9 ± 0.5	3.8 ± 0.4
Potassium level 3.0–3.5 mEq/l [c]	27 (25.2)	8 (21.6)	19 (27.1)

*$P = 0.0063$; **$P = 0.0003$
[a]Two patients without information on race
[b]One patient with missing BMI information
[c]Four patients with missing potassium levels

associated with calculated QTc ($r^2 = 0.17$, $P < 0.0001$): clozapine treatment ($P = 0.0016$), age 44 or older ($P = 0.0023$), and treatment with ziprasidone ($P = 0.036$).

Discussion

This case-control study indicates that treatment with two atypical antipsychotics does not appear to be associated with a significantly elevated QTc interval or QTc dispersion, despite the fact that patients receiving antipsychotic polytherapy were treated with significantly greater chlorpromazine-equivalent dosages. The average QTc of 403 ms observed in the 38 patients receiving two atypical antipsychotics was identical to the average QTc of 403 ms reported in a smaller sample of patients receiving antipsychotic polytherapy [9]. The number of patients with QTc prolongation was small and similar among patients treated with one or two atypical antipsychotics in our study. The results challenge the common assumption that antipsychotics prolong myocardial repolarization in a dose-dependent manner, at least as long as the total dosage remains moderate.

The global and adjacent QTc dispersion in patients treated with atypical antipsychotics have not been examined in prior studies. A QTc dispersion greater than 120 ms is a strong correlate of inducible monomorphic ventricular tachycardia and its pre-

Table 2 Electrocardiographic findings of patients treated with specific atypical antipsychotics combinations

Individual antipsychotic combinations	*N*	Machine QTc	Calculated QTc	Calculated QTc global dispersion	Calculated QTc adjacent dispersion
Olanzapine + quetiapine	9	407.0 ± 30.8	403.9 ± 36.5	43.6 ± 25.1	38.1 ± 21.0
Risperidone + aripiprazole	5	391.4 ± 7.9	397.4 ± 14.9	52.0 ± 17.4	46.2 ± 20.8
Olanzapine + risperidone	4	404.3 ± 11.7	398.3 ± 13.9	34.5 ± 12.2	31.0 ± 9.5
Quetiapine + ziprasidone	4	400.3 ± 12.8	405.8 ± 22.8	60.0 ± 20.1	54.8 ± 21.7
Clozapine + risperidone	3	405.7 ± 9.0	405.7 ± 3.5	80.7 ± 16.3	51.0 ± 25.2
Risperidone + quetiapine	3	386.3 ± 12.2	386.3 ± 30.1	56.3 ± 30.5	57.3 ± 14.7
Clozapine + olanzapine	2	333.5 ± 48.8	420.5 ± 54.4	36.0 ± 17.0	24.0 ± 0.0
Clozapine + quetiapine	2	415.5 ± 3.5	407.0 ± 2.8	87.5 ± 17.7	62.5 ± 17.7
Olanzapine + ziprasidone	2	422.5 ± 23.3	418.5 ± 31.8	53.0 ± 41.0	41.0 ± 25.5
Olanzapine + aripiprazole	1	362	382	77.0	77.0
Quetiapine + aripiprazole	1	395.0	409.0	48.0	48.0
Risperidone + ziprasidone	1	450.0	413.0	43.0	43.0
Ziprasidone + aripiprazole	1	435.0	406.0	20.0	20.0

dictive value is not influenced by sex, mean QTc, and left ventricular systolic function [1]. In contrast, no patient who had a QTc dispersion <90 ms experienced tachycardia during programmed ventricular stimulation. The normal results observed in our polytherapy group suggest that treatment with two atypical antipsychotics is unlikely to increase the rate of ventricular arrhythmias via this mechanism.

Our study is limited by its moderate sample size and cross-sectional design. Therefore, the results should be interpreted with caution, particularly given the absence of electrocardiographic data preceding the initiation of atypical antipsychotic treatment, reliance on only one electrocardiographic recording, and lack of drug blood levels at the time of admission. These issues are important in view of documented intraindividual variability of QTc intervals [10]. We also acknowledge the relatively low doses of ziprasidone prescribed to our patients, because this drug is known to produce significant QT prolongation [4]. Nevertheless, it is the largest study to date comparing QTc in patients on antipsychotic polytherapy vs. monotherapy and the first to evaluate the QTc dispersion in a population with mixed psychiatric disorders and a variety of two-antipsychotic drug combinations.

Our findings suggest that atypical antipsychotic polytherapy is not likely to lead to clinically significant changes in myocardial repolarization. Therefore, it is possible that the excess of cardiac mortality described in patients on two antipsychotics [6, 12] is due to different reasons. These are likely to include traditional risk factors for coronary heart disease, such as obesity, dyslipidemia, hyperglycemia and the metabolic syndrome, which are more prevalent in chronic and severely ill patients for whom clinicians choose antipsychotic polypharmacy [2, 8]. Long-term, prospective studies are required to assess the electrophysiologic effect of antipsychotic combinations and the contribution of myocardial repolarization abnormalities to the increased mortality of patients receiving antipsychotic polytherapy and must include large number of patients prescribed antipsychotics with the greatest potential for QTc prolongation.

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