QT Interval Duration and Dispersion in Children and Adolescents Treated With Ziprasidone

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Objective: To assess the incidence of symptoms (palpitations, syncope) and electrocardiographic signs (increased QT duration and dispersion) of an increased risk of torsades de pointes in youth treated with ziprasidone.

Method: Data for this study were collected as part of a prospective, observational, mixed inpatient and outpatient cohort study of youth who were administered antipsychotic treatment for the first time. For this study, we focus on 29 patients (mean ± SD age 15.3 ± 2.9 years) receiving ziprasidone (112.8 ± 50.6 mg/d; range, 20–240) for 99.3 ± 108.7 days. All patients had normal electrocardiograms (ECGs) and no serious medical illness at baseline. Patients had a mean of 2.7 ± 1.3 (median = 3; range, 1–7; total = 49) follow-up ECGs performed monthly for 3 months and every 3 months thereafter, with concurrent blood ziprasidone level measurements. Heart rate–corrected QT interval (QTc) duration and dispersion were measured manually in ≥ 6 ECG leads. QTc > 450-millisecond or ≥ 60-millisecond increase and QTc dispersion > 100 milliseconds were considered abnormal. The study was conducted from December 2001 to September 2007.

Results: No patient reported syncope or symptomatic arrhythmias. Seven patients (24.1%) developed ECG abnormalities; 5 had peak QTc durations > 450 milliseconds, and 2 had peak QTc dispersion > 100 milliseconds. The baseline-to-peak QTc duration increased by 22.9 ± 21 milliseconds ($P < .0001$). The baseline-to-peak QTc dispersion increased by 6.1 ± 31.4 milliseconds ($P = .30$). The peak QTc duration and dispersion occurred after 47.6 ± 46.0 and 60.4 ± 73.2 treatment days, respectively. Baseline-to-peak QTc duration and dispersion changes were not correlated with ziprasidone dose ($P = .65$) or plasma levels ($P = .50$).

Conclusions: Ziprasidone was associated with a dose- and level-independent, significant prolongation of QTc duration in one-quarter of youth. However, prolongation of QTc dispersion was nonsignificant, and no patient experienced concomitant abnormal prolongation of both QTc duration and QTc dispersion. The dissociation between prolonged QTc duration and dispersion suggests low arrhythmogenic potential in youth with normal baseline ECGs.

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Ziprasidone is a second-generation antipsychotic with proven effectiveness for pediatric bipolar disorder, Tourette's syndrome, pervasive developmental disorder, and obsessive-compulsive disorder.[1–3] In addition to high-affinity antagonist activity at 5-HT_{2A} and dopamine D_2 receptors, this antipsychotic has partial agonist activity at 5-HT_{1A} receptors and affinity for norepinephrine and serotonin transporters.[4] Ziprasidone is associated with substantially less weight gain and adverse metabolic effects than most other widely used atypical antipsychotics both in adults[5] and in youth[1,6] and is considered a reasonable treatment choice for minimizing these metabolic complications.[6] However, ziprasidone has the potential to prolong the heart rate–corrected QT interval (QTc) in the electrocardiogram (ECG). This effect is greater than the QTc prolongation observed during treatment with haloperidol, risperidone, olanzapine, and quetiapine.[7,8] Significant prolongation of QTc is generally considered a risk factor for torsades de pointes, ventricular fibrillation, and sudden death, particularly when the QTc is greater than 500 milliseconds.[9–11]

Antipsychotics produce QTc prolongation by blocking the rapid component of the delayed rectifier current, which promotes potassium efflux from the ventricular myocytes during repolarization.[10,11] The mechanism is similar to the QTc prolongation produced by many widely used drugs, such as the antiarrhythmic agents amiodarone and sotalol, quinolone and macrolide antibiotics, and methadone.[11] The incidence of torsades de pointes in patients treated with these drugs is extremely low, a fact that raises doubts about the value of QTc prolongation as the single electrocardiographic predictor for the risk of torsades de pointes. On the other hand, the risk of torsades de pointes is clearly increased when the QTc prolongation is associated with a concurrent prolongation of the intramyocardial dispersion of repolarization.[10] A larger difference between the action potential duration in adjacent regions of the ventricular myocardium enables circular reentry activity between areas with delayed repolarization and those with excitable myocytes.[10,12] The phenomenon is assessed by measuring the QTc dispersion, ie, the interlead variability of QTc on the ECG. A QTc dispersion > 120 milliseconds was shown to be a strong correlate of inducible ventricular tachycardia, and its predictive value was not influenced by gender, mean QTc, and left ventricular systolic

function.[13] QTc dispersion is also a stronger predictor for cardiovascular mortality than QTc duration in the general population,[14] patients with myocardial infarction,[15] subjects with congenital long QT syndromes,[16] and patients who developed torsades de pointes after intravenous administration of haloperidol.[17]

A 4-year postmarketing evaluation[4] and a 1-year randomized comparison between ziprasidone and olanzapine in 18,000 adult patients, resulting in similar nonsuicide-related death rates of 0.9% in both groups,[18] have indicated that the ziprasidone-induced QTc prolongation is not linked to the occurrence of torsades de pointes in adults, and only one case of torsades de pointes related to treatment with ziprasidone has been reported in the literature.[19] Although one case of sudden death in a child treated with ziprasidone was reported, the authors made it clear that they believed after extensive investigation that this death was unrelated to the ziprasidone treatment.[20]

In contrast to the large adult databases,[4,18] the effect of ziprasidone on myocardial repolarization in children and adolescents has been reported only in a total of 102 patients who were included in 5 published, open-label studies.[1–3,21,22] In these studies, the mean QTc change ranged from –3 milliseconds to +28 milliseconds, and none of these pediatric patients was reported to have experienced syncope or other cardiovascular events. The QTc dispersion was not assessed in any of these studies.

In this prospective study, we evaluated the QTc duration and QTc dispersion in 29 children and adolescents monitored carefully during treatment with ziprasidone. On the basis of absence of ziprasidone-related torsades de pointes cases after 8 years of clinical use, we hypothesized that ziprasidone has a low torsadogenic potential because the drug-induced QTc prolongation is not accompanied by a concomitant increase in QTc dispersion.

METHOD

Setting and Patient Population

Data required for this study were collected as part of the Second-Generation Antipsychotic Treatment: Indications, Effectiveness and Tolerability in Youth (SATIETY) study,[23] a prospective, observational cohort study of antipsychotics in pediatric patients treated for psychotic, mood, or aggressive spectrum disorders. Subjects were recruited from the child and adolescent inpatient and outpatient services of Zucker Hillside Hospital and Schneider's Children Hospital, North Shore-Long Island Jewish Health System, New York, and from community-based psychiatrists in the catchment areas of these hospitals. The study was conducted from December 2001 to September 2007.

Subject Eligibility

Patients aged 4–19 years were eligible for the study if they had started ziprasidone monotherapy within 7 days of the baseline assessment and had an ECG obtained at baseline and at a minimum of 1 follow-up visit that included an ECG. Exclusion criteria were baseline QTc > 500 milliseconds (n = 0), eating disorders, severe medical illness, pregnancy, breastfeeding, and expected move out of the area within 1 month of starting treatment with ziprasidone. Written informed consent was obtained from patients older than 18 years of age or from legal guardians if the patient was a minor. According to the institutional review board rules, patients older than 8 years of age gave informed assent. The patients' mental health care providers selected ziprasidone and adjusted doses of ziprasidone and other psychotropic drugs based on clinical need. The research protocol was approved by the Institutional Review Board, North Shore-Long Island Jewish Health System, Manhasset, New York.

Assessment of Ziprasidone and Potassium Levels

Ziprasidone and potassium levels were measured in blood samples drawn between 7–11 AM after at least 8 hours fasting at baseline, monthly for the first 3 months and quarterly thereafter. Ziprasidone levels were assessed at the Thomas Cooper Laboratory, Nathan Kline Research Institute, Orangeburg, New York, using liquid chromatography on sera that had been stored at –40°C. Plasma potassium was measured spectrophotometrically at the North Shore Core Laboratory, Manhasset, New York, on the same day of the blood draw.

Measurement of QTc Duration and Dispersion

All patients had a 12-lead ECG recorded with the same instrument (ELI 1200, Mortara Instruments, Milwaukee, Wisconsin) at baseline, monthly for the first 3 months and quarterly thereafter. All follow-up ECGs and the vast majority of baseline ECGs were obtained at the same time as the Morning fasting blood samples. However, a small number of patients had their baseline ECGs obtained at different times upon hospital admission. The electrocardiograph is programmed to calculate the "automated" QTc. Two board-certified internists (V.F. and P.M.) with extensive clinical and research experience in the evaluation of ECGs in adults and children and adolescents[24] measured the QT intervals in at least 6 leads in which the onset of the QRS complex and the return of T wave to baseline could be clearly identified. These physicians were provided numerically coded ECGs and had no access to demographic or clinical data. The QT duration was corrected for heart rate according to the Bazett formula[9] and averaged for all assessed leads. QTc dispersion was calculated as the difference between the longest and shortest individual lead QTc.[13] QTc was considered prolonged if greater than 450 milliseconds or 60 milliseconds longer than at baseline.[9] QTc dispersion was considered abnormal if greater than 100 milliseconds.[13]

Data Analyses

Analyses of variance and χ^2 tests were performed for continuous and categorical variables, respectively. The relationships between QTc duration and QTc dispersion with ziprasidone dose, serum ziprasidone level, and plasma potassium level

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Table 1. Baseline Demographic and Clinical Characteristics of 29 Children and Adolescents Treated With Ziprasidone

Characteristic	Total (n = 29)	Normal QTc Duration and QTc Dispersion (n = 22)	Abnormal QTc Duration or QTc Dispersion (n = 7)	*P* Value
Demographic characteristics				
Age, mean ± SD, y	15.3 ± 2.9	15.5 ± 2.9	14.8 ± 3.0	.60
Adolescents (age 12 y or older), n (%)	25 (86.2)	19 (86.4)	6 (85.7)	.96
Male gender, n (%)	13 (44.8)	10 (45.5)	3 (42.9)	.90
Ethnicity, n (%)				.13
White	14 (48.3)	9 (40.9)	5 (71.4)	
African-American	8 (27.6)	8 (36.4)	0 (0.0)	
Hispanic	5 (17.2)	4 (18.2)	1 (14.3)	
Other	2 (6.9)	1 (4.5)	1 (14.3)	
Weight, mean ± SD, lb	163.5 ± 47.9	171.4 ± 50.5	143.0 ± 36.2	.35
BMI (kg/m^2), mean ± SD	27.6 ± 5.9	28.3 ± 6.2	25.8 ± 4.7	.96
BMI percentile, mean ± SD	85.6 ± 21.7	85.7 ± 22.7	85.3 ± 19.1	.96
Psychiatric diagnosis, n (%)				
Disruptive behavior disorders (ODD/CD/IED/ICD[a])	16 (55.2)	10 (45.5)	6 (85.7)	.06
Attention-deficit/hyperactivity disorder	11 (37.9)	8 (36.4)	3 (42.9)	.76
Psychosis not otherwise specified	8 (27.6)	7 (31.8)	1 (14.3)	.37
Bipolar disorder	7 (24.1)	5 (22.7)	2 (28.6)	.75
Autism spectrum disorder	6 (20.7)	3 (13.6)	3 (42.7)	.09
Schizophrenia/schizoaffective disorder	5 (17.2)	4 (18.2)	1 (14.3)	.81
Mood disorder not otherwise specified	3 (10.3)	2 (9.1)	1 (14.3)	.68
Anxiety disorders	2 (6.9)	2 (9.1)	0 (0.0)	.41
Substance used disorder	2 (6.9)	1 (4.5)	1 (14.3)	.37
Major depression	1 (3.5)	1 (4.5)	0 (0.0)	.57
Clinical Global Impression-Severity of Illness score, mean ± SD	5.1 ± 0.9	5.1 ± 0.9	5.1 ± 0.9	.83
Global Assessment of Functioning score, mean ± SD	39.2 ± 10.6	39.6 ± 10.7	38.4 ± 10.5	.81

[a]Not otherwise specified.
Abbreviations: BMI = body mass index, CD = conduct disorder, ICD = impulse-control disorder, IED = intermittent explosive disorder, ODD = oppositional defiant disorder, QTc = heart rate–corrected QT interval.

were assessed with Pearson product-moment correlation coefficients. All tests were 2-sided, with α set at < .05 and calculated with JMP 5.0.1, 1989–2003, (SAS Institute Inc, Cary, North Carolina).

RESULTS

Demographic and Clinical Characteristics

Twenty-nine pediatric patients (mean ± SD age = 15.3 ± 2.9 years, 44.8% male, 48.3% white) participated in the study. The 3 most common diagnostic categories were disruptive behavior disorders (ie, intermittent explosive disorder [IED], conduct disorder, oppositional defiant disorder [ODD], and impulse-control disorder not otherwise specified) (55.2%), attention-deficit/hyperactivity disorder (37.9%), and psychosis not otherwise specified (27.6%) (Table 1). Patients were treated with ziprasidone at a mean ± SD maximum dose of 112.8 ± 50.6 mg/d (median = 80 mg/d; range, 20–240 mg/d) and remained in the study for 99.3 ± 108.7 days. The highest mean ± SD daily dose of ziprasidone at the time of an ECG was 89.9 ± 52.3 mg (range, 20–180 mg). (The discrepancy between the mean clinical dose of ziprasidone and the dose at the time of the ECG assessment is due to the fact that patients were treated with flexible ziprasidone doses that could be titrated and adjusted during the study and that were sometimes lower at the ECG assessment time point.) In addition to ziprasidone, patients were also treated with mood stabilizers (41.4%), antidepressants (17.2%), anxiolytic/hypnotics (13.8%), and psychostimulants (13.8%) (Table 2).

Global QTc Changes

Patients had a mean ± SD of 2.7 ± 1.3 (median = 3; range, 1–7; total = 49) follow-up ECGs after baseline. At baseline, the mean ± SD QTc duration and dispersion were 410.5 ± 25.0 milliseconds and 47.0 ± 24.8 milliseconds, respectively (Table 3). During the study, the mean ± SD peak QTc duration was 433.4 ± 25.1 milliseconds (mean change = 22.9 ± 21 milliseconds, $P < .0001$), while the mean peak QTc dispersion was 53.1 ± 26.6 milliseconds (mean change = 6.1 ± 31.4 milliseconds, $P = .30$). The mean ± SD duration of treatment at the time of the longest QTc duration and dispersion was 47.6 ± 46.0 days and 60.4 ± 73.2 days, respectively (Table 2).

The change from baseline QTc to the peak QTc duration did not correlate with ziprasidone dose (29 ECGs: $R^2 = 0.0079$, $P = .65$, Figure 1A) or serum ziprasidone levels (18 ECGs: $R^2 = 0.0013$, $P = .89$, Figure 1B). Results were similar for the correlations between QTc changes in all available ECGs and ziprasidone dose (78 ECGs: $R^2 = 0.0059$, $P = .50$) and serum ziprasidone level (51 ECGs: $R^2 = 0.000052$, $P = .96$). Likewise, there were no significant correlations between changes from baseline-to-peak QTc dispersion and ziprasidone dose (29 ECGs: $R^2 = 0.047$, $P = .26$, Figure 2A) and serum ziprasidone level (18 ECGs: $R^2 = 0.029$, $P = .50$, Figure 2B). Results were similar for the correlations between QTc dispersion changes in all available ECGs and ziprasidone dose (78 ECGs: $R^2 = 0.0040$, $P = .79$), and serum ziprasidone level (51 ECGs: $R^2 = 0.069$, $P = .063$). Finally, potassium levels were also not correlated with QTc duration

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Table 2. Treatment and Outcome Characteristics of 29 Children and Adolescents Treated With Ziprasidone

Characteristic	Total (n = 29)	Normal QTc Duration and QTc Dispersion (n = 22)	Abnormal[a] QTc Duration or QTc Dispersion (n = 7)	*P* Value
Ziprasidone treatment, mean ± SD				
Duration of ziprasidone treatment, d	99.3 ± 108.7	96.1 ± 97.8	109.4 ± 146.7	.78
Highest daily dose of ziprasidone at time of ECG, mg	89.0 ± 52.3	98.2 ± 49.7	60.0 ± 52.9	.09
Mean serum ziprasidone level, μg/L[b]	108.8 ± 75.3	109.3 ± 66.2	107.5 ± 104.6	.96
Comedications at longest QTc				
Total no. of comedications, mean ± SD	1.48 ± 0.85	1.45 ± 0.86	1.57 ± 1.13	.77
Patients on > 2 psychotropic medications, n (%)	12 (41.4)	7 (31.8)	5 (71.4)	.06
Mood stabilizers, n (%)	12 (41.4)	8 (36.4)	4 (57.4)	.09
Antidepressants, n (%)	5 (17.2)	5 (20.0)	0 (0.0)	.16
Anxiolytics/hypnotics, n (%)	4 (13.8)	4 (16.0)	0 (0.0)	.22
Psychostimulants, n (%)	4 (13.8)	3 (13.6)	1 (14.3)	.19
Anticholinergics, n (%)	2 (6.9)	2 (9.1)	0 (0.0)	.40
Other psychotropics, n (%)[c]	4 (13.8)	3 (13.6)	1 (14.3)	.97
Longest QTc, mean ± SD				
Duration of treatment at longest QTc, d	47.6 ± 46.0	48.2 ± 48.9	45.7 ± 33.2	.90
Daily ziprasidone dose at longest QTc, mg	71.3 ± 48.2	76.5 ± 47.0	54.3 ± 52.6	.29
Serum ziprasidone level at longest QTc, μg/L[d]	70.1 ± 51.4	67.1 ± 36.1	78.6 ± 96.5	.70
Longest QTc dispersion, mean ± SD				
Duration of treatment at longest QTc dispersion, d	60.4 ± 73.2	63.6 ± 81.4	51.4 ± 37.1	.69
Daily ziprasidone dose at longest QTc dispersion, level, mg	77.4 ± 49.7	84.4 ± 49.7	57.5 ± 49.5	.20
Serum ziprasidone level at longest QTc dispersion, level[e], μg/L	66.1 ± 68.2	61.7 ± 41.8	82.3 ± 101.3	.55

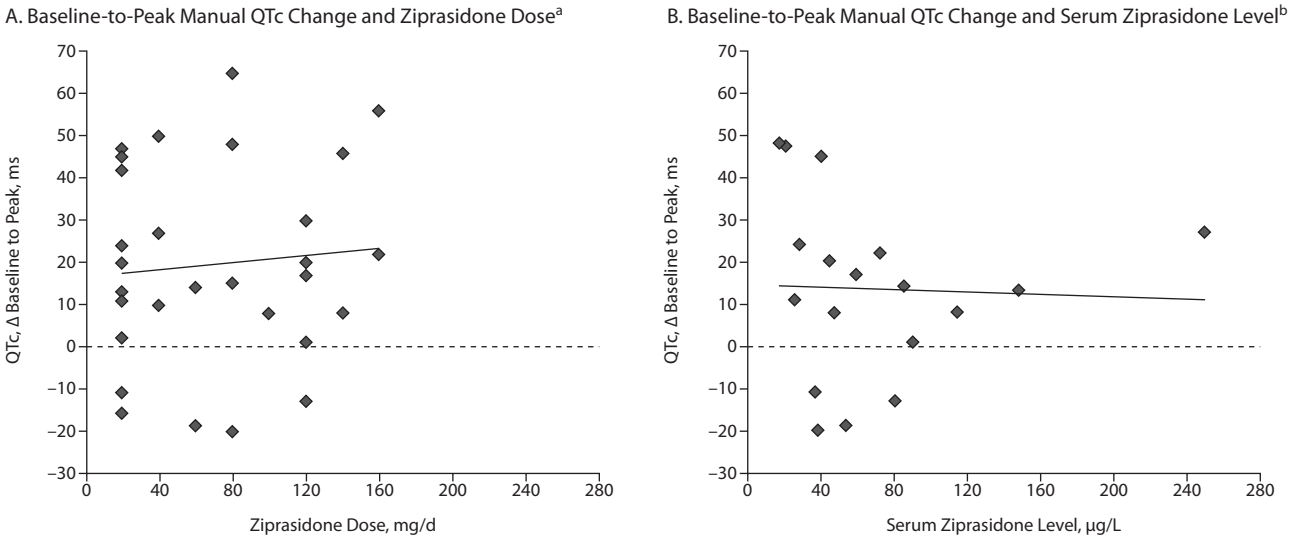
[a]QTc was considered prolonged if greater than 450 milliseconds or 60 milliseconds longer than at baseline.[9] QTc dispersion was considered abnormal if greater than 100 milliseconds.[13]
[b]Based on 19 patients (14 with normal QTc and 5 with abnormal QTc).
[c]Other psychotropic medications: α_2 agonists, β-blockers, antihistamines.
[d]Based on 19 patients (14 with normal QTc and 5 with abnormal QTc).
[e]Based on 19 patients (17 with normal QTc and 2 with abnormal QTc).
Abbreviations: ECG = electrocardiogram, QTc = heart rate–corrected QT interval.

Table 3. Electrocardiographic Changes Between Baseline and Peak Values in 29 Children and Adolescents Treated With Ziprasidone for up to 62 Weeks

	Baseline		Peak Value		Change		
ECG Parameter	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	*P* Value
Heart rate, bpm	82.7 ± 11.8	62 to 108	78.6 ± 20.2	62 to 113	−4.1 ± 21.9	−48 to 37	.32
QRS, ms	87.9 ± 9.5	70 to 106	93.9 ± 10.6	72 to 124	6.0 ± 8.3	−10 to 28	.0005
QTc, ms	410.5 ± 25.0	371 to 460	433.4 ± 25.1	383 to 507	22.9 ± 21.0	−20 to 68	< .0001
QTc dispersion, ms	47.0 ± 24.8	11 to 118	53.1 ± 26.6	3 to 103	6.1 ± 31.4	−53 to 59	.30

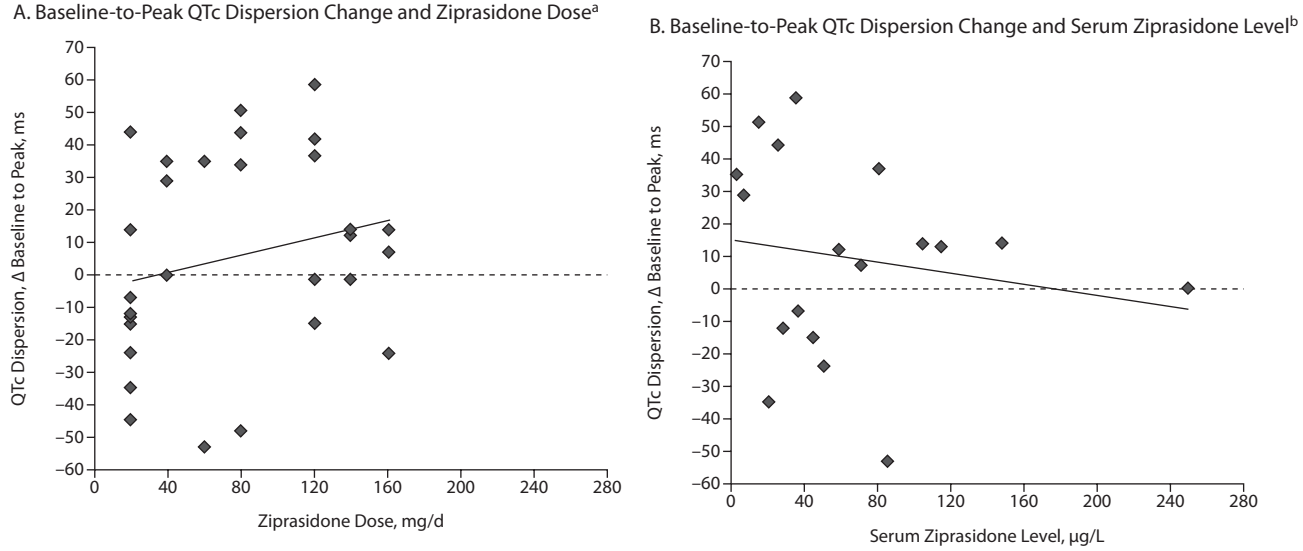
Abbreviations: bpm = beats per minute, ECG = electrocardiogram, QTc = heart rate–corrected QT interval.

Figure 1. Correlation Between Baseline-to-Peak QTc Duration Change and Ziprasidone Dose and Serum Level



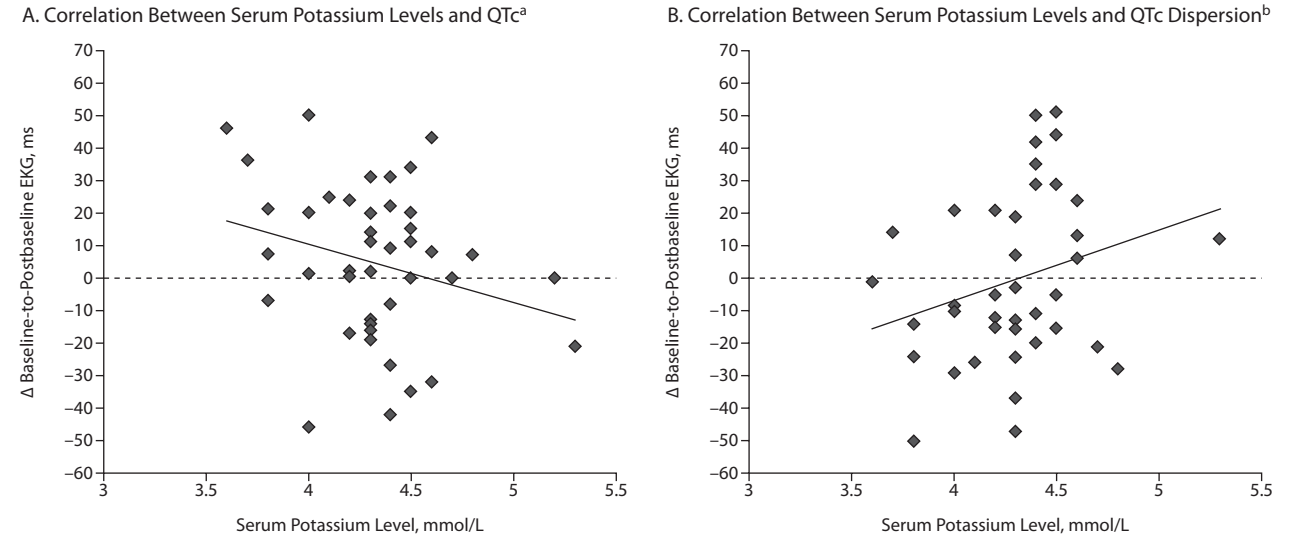
[a]$R^2 = 0.0079$, $P = .65$.
[b]$R^2 = 0.0013$, $P = .89$ (based on data from 18 patients with available serum ziprasidone levels).
Abbreviation: QTc = heart rate–corrected QT interval.

Figure 2. Correlation Between Baseline-to-Peak QTc Dispersion Change and Ziprasidone Dose and Serum Level



[a] $R^2 = 0.047$, $P = .26$.
[b] $R^2 = 0.029$, $P = .50$ (based on data from 18 patients with available ziprasidone serum levels).
Abbreviation: QTc = heart rate–corrected QT interval.

Figure 3. Correlation Between Serum Potassium Levels and QTc and QTc Dispersion



[a] $R^2 = 0.073$, $P = .084$.
[b] $R^2 = 0.066$, $P = .10$.
Abbreviations: ECG = electrocardiogram, QTc = heart rate–corrected QT interval.

(42 ECGs: $R^2 = 0.07323$, $P = .084$, Figure 3A) or QTc dispersion (41 ECGs: $R^2 = 0.066$, $P = .10$, Figure 3B).

Patients With Clinically Significant QTc Changes

Seven patients (24.1% of the sample) had clinically significant changes in QTc duration or QTc dispersion. In 5 patients (17.2%), the QTc was prolonged to >450 milliseconds; 1 of these patients had a peak QTc >500 milliseconds and 1 had a peak QTc prolonged by more than 60 milliseconds compared with baseline. Two patients increased their QTc dispersion to values >100 milliseconds. Patients with (n = 7) and without (n = 22) clinically significant QTc changes during treatment with ziprasidone were similar with regard to demographic, illness, and treatment variables (Table 3).

DISCUSSION

In this prospective study of 29 children and adolescents receiving ziprasidone for a variety of psychiatric disorders, the baseline-to-peak QTc duration increased significantly

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and exceeded in 5 patients 450 milliseconds. In contrast, changes in QTc dispersion in the entire sample were modest and statistically insignificant. Two patients acquired QTc dispersion greater than 100 milliseconds. There were no reports of syncope or symptomatic arrhythmias, and the peak QTc prolongation occurred earlier than the peak QTc dispersion. None of the 29 patients had both a prolonged QTc and an abnormal QTc dispersion during ziprasidone treatment at an average daily dose of 112 mg, followed for an average of 99 days. The concomitant use of other psychotropic drugs was not different in patients with or without myocardial repolarization changes during treatment with ziprasidone.

The finding of increased QTc duration with ziprasidone is consistent with studies in adults[7] and in youth treated with ziprasidone.[1–3,21,22] While prior studies in youth resulted in a broad range of mean QTc changes (ie, −3 milliseconds to +28 milliseconds),[1–3,21,22] varying methodologies of using baseline-to-endpoint or baseline-to-peak QTc values may be responsible for these differences. Nevertheless, the 23-millisecond mean increase found in our study is still within the previously reported range. Furthermore, previously reported QTc prolongation (defined as incidence of QTc > 450 milliseconds or > 460 milliseconds) in youth receiving ziprasidone in the aforementioned studies have ranged from 0% (ie, 0/12[3] and 0/21)[22] to 15.0% (ie, 3/20),[21] which was lower than our rate of 24.1%. For additional comparison, 6 months of treatment in 38 children and adolescents (mean age = 15.1[4–18] years, 68.4% male, 92.1% Caucasian) with risperidone (n = 12, mean dose = 2.4 mg [range, 0.4–5]), olanzapine (n = 8, mean dose = 10.9 mg [range, 5–25]), or quetiapine (n = 18, mean dose = 469 mg [range, 100–1500]) was associated with a mean QTc prolongation of 6.3 ± 25.5 milliseconds (range, −38.0 to 70.0 milliseconds) for the combined group.[8] However, the authors did not report the percentage of patients with newly emerging QTc abnormalities, precluding a comparison with our ziprasidone-treated pediatric sample. Moreover, as in all other prior studies of antipsychotic-related QTc changes in pediatric patients, no QTc dispersion values were reported in that study either.

The fact that there were no significant changes in QTc dispersion in this sample of children and adolescents treated with ziprasidone is encouraging. In epidemiologic studies using cardiovascular deaths as a surrogate marker for fatal arrhythmias, prolonged QTc and increased QTc dispersion were significant predictors of all-cause mortality and cardiovascular mortality.[14] However, after the researchers controlled for coronary risk factors, only QTc dispersion and not QTc prolongation remained a strong predictor of cardiovascular mortality.[14] Likewise, a controlled study comparing patients with and without torsades de pointes after intravenous administration of haloperidol found that QTc dispersion was significantly greater in patients who experienced torsades de pointes, particularly when associated with a QTc duration > 500 milliseconds.[17] Thus, the absence of any clinical or electrocardiographic evidence for arrhythmias in our youth treated with ziprasidone, including one-quarter who developed electrocardiographic abnormalities of QTc or QTc dispersion, suggests that the absence of concurrently abnormal QTc dispersion and QTc prolongation might be protective. The same reason might be responsible for the lack of increased cardiac death rates with ziprasidone in adults treated with ziprasidone.[18] Although the absence of clinically relevant arrhythmias associated with ziprasidone in our sample could be due to lack of power for its detection, our results and the general conclusions that the cardiac risk potential of ziprasidone that does not seem to be elevated compared to other first-line antipsychotics despite greater numeric increase in QTc seems to be supported by a recently completed, large-scale study. In the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC), an open-label, randomized, postmarketing simple trial, 18,154 patients with schizophrenia were randomized to ziprasidone (n = 9,077) or olanzapine (n = 9,077).[25] At the end of the 1-year trial, both medications were associated with an identical and low nonsuicide mortality rate of 0.9% (odds ratio = 1.0; 95% CI, 0.76–1.39).[25] Moreover, even after readjudication, specific cardiac mortality rates did not differ among the 2 antipsychotics in this large, randomized sample.

Nevertheless, our findings need to be interpreted within the limitations of this prospective study, including the relatively small sample size, ECG assessments that were not conducted at the same time in the morning and in a fasting status in all patients, allowance of clinically indicated comedications, and absence of a placebo group. Research studies reporting on QTc intervals have been the object of methodological scrutiny in light of the recommendations of the 2005 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,[26] and inclusion of a placebo comparator has been recommended to avoid assessment biases. In our case, we avoided this pitfall by having all QTc intervals measured by experts blinded to baseline or intratreatment origin of the tracings. In addition, the QT correction for rate according to the Bazett's formula could produce "longer" QTc at higher heart rates and "shorter" QTc at lower heart rates. However, this limitation does not apply to our study because the mean heart rate did not change from baseline to the time of the peak QTc. Therefore, in this group of pediatric patients with normal baseline ECG, the observed changes are highly likely related to the use of ziprasidone. We also acknowledge the limitation created by obtaining a single baseline ECG.

The fact that QT prolongation alone is not sufficient for the emergence of torsades de pointes has been convincingly demonstrated in studies evaluated amiodarone, the most widely used antiarrhythmic drug. Although amiodarone produces substantial QT prolongation, it has not been associated with torsades de pointes, a fact attributed to lack of effect on transmyocardial dispersion of repolarization.[27]

In conclusion, our findings suggest that ziprasidone-induced changes in QTc duration and dispersion seem to occur independent of each other in a population of children and adolescents without significant medical illnesses. This

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temporal dissociation may explain why ziprasidone has not been associated with the production of torsades de pointes, ventricular arrhythmias, or sudden death in children and adolescents and why there have been no increased sudden cardiac death rates with ziprasidone compared to other first-line antipsychotics in adults. The data question the need for electrocardiographic monitoring of youth treated with ziprasidone who have a normal ECG prior to taking this antipsychotic drug, are physically healthy, and have no family history of premature cardiac death. Moreover, these data suggest that ziprasidone's advantage of producing relatively limited increase in adiposity and metabolic abnormalities in youth[6] should be given more weight than the effect on QTc prolongation when considering its use in clinical practice.

Drug names: amiodarone (Nexterone, Pacerone, and others), haloperidol (Haldol and others), methadone (Methadose, Dolophine, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), sotalol (Betapace, Sorine, and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Correll** has been a consultant and/or advisor to or has received honoraria from Actelion, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ortho-McNeil/Janssen/Johnson & Johnson, Merck, Otsuka, and Pfizer. **Dr Malhotra** has been a consultant to Vanda, Wyeth, PGx Health, and Eli Lilly; has received grant/research support from Eli Lilly; and has served on speakers or advisory boards for Bristol-Myers Squibb. **Dr Kane** has been a consultant to Janssen, AstraZeneca, Pfizer, Eli Lilly, Vanda, Bristol-Myers Squibb, and Otsuka and has served on speakers or advisory boards for Bristol-Myers Squibb, Otsuka, Eli Lilly, and Janssen. **Dr Manu** has received speaker's honoraria from Eli Lilly and Bristol-Myers Squibb. **Drs Lops** and **Figen** report no financial or other conflicts of interest.

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