Antipsychotic Drug Administration Does Not Correlate with Prolonged Rate-Corrected QT Interval in Children and Adolescents: Results from a Nested Case–Control Study

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Abstract

Background: The rate-corrected QT interval (QTc) prolongation is a risk factor for sudden cardiac death and may be induced by antipsychotic drugs.

Objective: To determine the clinical characteristics associated with QTc prolongation (440 msec or greater) in children and adolescents hospitalized for treatment of psychiatric disorders.

Method: We determined the frequency of baseline prolongation of QTc in 811 psychiatric pediatric inpatients (15.5 ± 2.4 years of age). QTc duration was 440 msec or greater (range 441–481 msec) in 16 patients (1.97%). In a 1:5 nested case–control design, the 16 patients with prolonged QTc were age- and gender-matched with 80 patients with QTc of <421 msec.

Results: Patients with normal and prolonged QTc had similar utilization of antipsychotics (43.8% vs. 40.8%) and daily chlorpromazine equivalents (165 ± 110 vs. 168 ± 218 mg). Hypokalemia ($p = 0.009$) and obesity ($p = 0.032$) were more common among patients with prolonged QTc. The correlation between obesity and QTc prolongation was confirmed in logistic regression analysis.

Conclusions: In a large cohort of youth hospitalized for treatment of psychiatric disorders, a prolonged QTc on admission was rare and correlated with the presence of obesity, but not with current use of antipsychotic drugs.

Introduction

ANTIPSYCHOTIC DRUGS ARE effective in children and adolescents with schizophrenia, bipolar disorder, autism, aggression, and tics (Varley and McClellan 2009). These drugs have a dose-dependent effect on the myocardial repolarization that may lead to prolongation of the rate-corrected QT interval (QTc), torsades de pointes, and sudden cardiac death (Vieweg 2002). The estimated incidence of sudden cardiac death in children and adolescents, excluding sudden infant death syndrome, is in the range 0.6–6.2/100,000 in the United States, but the precise contribution of the long QT syndrome (congenital or acquired) to these events is not known (Gajewski and Saul 2010).

The benefit of electrocardiographic screening for QTc prolongation in pediatric populations requiring antipsychotics is not known. In this study we evaluated a cohort of pediatric psychiatric inpatients to determine the prevalence of QTc prolongation and to investigate associations between QTc duration and the utilization of antipsychotics.

Methods

Data for this study were collected from the records of 826 individual patients aged 7–18 years who were consecutively evaluated in the admissions unit and hospitalized over a 10-year period (2000–2009) to a single 230-bed acute care psychiatric hospital. The hospital policy requires a 12-lead electrocardiogram (ECG) on the day of admission. All ECGs were recorded at the same paper speed (25 mm/sec) with the same type of instrument (ELI 1200; Mortara Instruments, Milwaukee, WI). The study was approved by the Institutional Review Board of the North Shore–Long Island Jewish Health System, Manhasset, NY.

We identified for each patient the earliest available ECG. Two medical consultants with extensive clinical and research experience in ECG interpretation measured the QT interval and calculated the QTc according to the Bazett's formula (Haddad and Anderson 2002). These physicians were provided numerically coded ECG's and had no access to demographic or clinical data. The QT was measured from the onset of QRS complex to the end of the T wave

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at the junction of the T-P line in at least three different leads of 12-lead ECGs recorded at a speed of 25 mm/sec. Tracings for 11 patients were not suitable for accurate interpretation and were excluded from the sample. During the period of clinical observation, none of these patients had evidence of symptomatic arrhythmias and none died suddenly.

The QTc was considered prolonged if >440 msec, regardless of gender, as recommended in the cardiology and pharmacological literature (Moss 1993; Haddad and Anderson 2002) and used in studies of children treated with tricyclic antidepressants (Wilens et al. 1996) and ziprasidone (Blair et al. 2005). This unisex threshold is at variance with findings from a community-based representative North American population that demonstrated a drop of 20 msec in QTc duration in adolescent males after puberty (Rautarhaju et al. 1992), but was used by us to allow comparisons with previous studies. In a nested case-control design, each patient with prolonged QTc was matched for sex and age, with five patients selected at random from among the 680 cases whose QTc was <420 msec.

The psychiatric (diagnoses, antipsychotic drug treatment, chlorpromazine equivalent of atypical and/or typical antipsychotic, and other psychotropic medications), anthropometric (body mass index), and biochemical (serum potassium) characteristics of patients with prolonged QTc were compared with those of the nested control subjects. The chlorpromazine equivalent of antipsychotics was calculated as 100 mg chlorpromazine equal 2 mg of risperidone, 5 mg of olanzapine, 75 mg of quetiapine, 60 mg of ziprasidone, 7.5 mg of aripiprazole (5), 2 mg of haloperidol, and 10 mg of molindone (Haase 1983; Woods 2003). Analyses of variance, chi-square test, and Fischer's Exact test determined the significance of univariate differences, with alpha set at <0.05 . Variables with differences significant at $p < 0.1$ were further analyzed with logistic regression. Data were processed with JMP 5.0.1., 1989–2003, SAS Institute, Inc, Cary, NC.

Results

Patients with prolonged QTc

The 811 children and adolescents (404 males and 407 females) included in this study had a mean age of 15.5 ± 2.4 years (range: 7.2–18.9 years). Overall, the QTc averaged 399.1 ± 20.1 msec (range: 313–481 msec) and was longer in females than in males (401.2 ± 20.7 msec vs. 397.0 ± 19.3 msec, $p = 0.0032$).

Six hundred ninety patients (85.1%; 95% CI: 82.5%–87.4%) had a QTc shorter than 420 msec and 105 (12.9%; 95% CI: 10.8%–15.4%) had a QTc in the 420–440 range. The proportion of females was lower among patients with QTc <420 msec ($p = 0.0013$), but greater in the subgroup with QTc 420–440 ($p = 0.0028$).

QTc > 440 msec (range: 442–481 msec; mean 454 ± 10 ; 95% CI: 449–460 msec) were identified in 16 patients (1.97%; 95% CI: 1.17%–3.25%). This group included 6 males and 10 females, that is, 1.49% of all males (95% CI: 0.31%–2.67%) and 2.46% of all females (95% CI: 0.96%–3.96%). The 80 age- and gender-matched nested control subjects had a mean QTc of 391 ± 21 msec (95% CI: 386–396 msec).

Psychiatric diagnoses and psychotropic drugs

Univariate comparisons of the psychiatric diagnoses and psychotropic treatments indicated that patients with prolonged QTc had a higher frequency of schizophrenia and of treatment with anxiolytic-hypnotic drugs and a lower incidence of major depressive disorder (Table 1).

Potassium levels

Blood samples were drawn for spectrophotometric electrolyte measurements on admission for 11 patients from the prolonged QTc group and 72 patients with normal QTc. The mean potassium levels were similar in the 2 groups (3.9 ± 0.4 vs 4.1 ± 0.4 mEq/L, $p = 0.09$). The frequency of hypokalemia (K level 3.5 mEq/L or lower) was greater in the prolonged QTc group (36.4% vs 8.1%, $p = 0.0093$).

Body mass index

The weight and height were recorded for 13 of the 16 patients with prolonged QTc and 72 of the 80 patients with normal QTc duration. The proportion of obese patients (i.e., ≥ 95 th BMI percentile) was significantly greater in the group with prolonged QTc (38.5% vs 13.9%, $p = 0.032$). The finding was confirmed by logistic regression ($p = 0.030$).

Discussion

The QTc prolongation was infrequent (1.97%) and mild (range: 441–481 msec) in a cohort of 811 children and adolescents who had EKGs recorded at the time of admission for hospital treatment of psychiatric disorders. Based on retrospective chart review, a nested case-control comparison of youth with prolonged QTc with gender- and age-matched patients with QTc < 420 msec indicated that obesity and hypokalemia were significantly more common among patients with QTc prolongation. In contrast, treatment with antipsychotic drugs, exposure to individual atypical antipsychotics, chlorpromazine equivalent doses of antipsychotic treatment, and exposure to other psychotropic medications were not associated with QTc prolongation. The results must be interpreted cautiously, because our study is limited by its cross-sectional design and absence of plasma levels of antipsychotic drugs.

The low prevalence of QTc prolongation in our pediatric cohort stands in stark contrast to the much higher prevalence of QT interval disturbance in older age groups (Lubart et al. 2009; Vieweg et al. 2009). Depending on sample selection and type correction for heart rate, the QTc was found to be prolonged in 27%–75% of hospitalized patients older than 60 years (Lubart et al. 2009). The explanation for the much lower rate of QTc prolongation in pediatric samples is undoubtedly the prevalence of heart disease, as 43% of the elderly with prolonged QTc had ischemic heart disease (Lubart et al. 2009), a condition rare in children and adolescents.

The higher frequency of hypokalemia among patients with prolonged QTc is not surprising, as this electrolyte disturbance delays myocardial repolarization (Haddad and Anderson 2002). Hypokalemia must be suspected in all pediatric patients with a frequent history of inadequate food intake, vomiting, diarrhea, or use of diuretics or laxatives. The association between obesity and QTc prolongation identified in our study confirms work demonstrating increased heterogeneity of ventricular repolarization in obese nonhypertensive children (Guvén et al. 2010; Nigro et al. 2010) and it is particularly worrisome, given the marked weight gain associated with atypical antipsychotic medications in children and adolescents (Correll et al. 2009; Varley and McClellan 2009).

Does a 2% prevalence of baseline QTc prolongation justify mandatory electrocardiographic screening of children and adolescents before the initiation of treatment with antipsychotics? We could not assess the future arrhythmic events in our cohort, but addressing a similar question about the use of psychostimulants, the American Academy of Pediatrics has found that “it has not been

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH PROLONGED RATE-CORRECTED QT INTERVAL AND AGE- AND GENDER-MATCHED SUBJECTS RANDOMLY SELECTED IN A NESTED 1:5 DESIGN

Characteristic	Total (n = 96)	Patients with QTc 440 msec or greater (n = 16)	Patients with QTc 420 msec or shorter (n = 80)	p value
Demographic variables				
Age (years $\pm$ SD)	15.3 $\pm$ 2.7	15.4 $\pm$ 3.0	15.3 $\pm$ 2.7	0.87
Sex (male, n, %)	36 (37.5)	6 (37.5)	30 (37.5)	1.00
Race (n, %)				0.56
White	40 (43.0)	9 (56.3)	31 (40.3)	
African American	31 (33.3)	3 (18.8)	28 (36.4)	
Hispanic	16 (17.2)	3 (18.8)	13 (16.9)	
Asian	6 (6.5)	1 (6.3)	5 (6.5)	
Psychiatric diagnoses (n, %)				
Depressive disorders	49 (51.0)	4 (25)	45 (56.3)	0.029
Bipolar disorder	24 (25.0)	7 (43.8)	17 (21.3)	0.058
ADHD	21 (21.9)	3 (18.8)	18 (22.5)	0.74
Oppositional-defiant & disorder	20 (20.8)	2 (12.5)	18 (22.5)	0.37
Mood disorder NOS	17 (17.7)	1 (6.3)	16 (20.0)	0.13
Substance use disorders	16 (16.1)	4 (25.0)	12 (15.0)	0.33
Anxiety disorders	7 (7.3)	1 (6.3)	6 (7.5)	0.86
Psychosis NOS	6 (6.3)	0 (0)	6 (7.5)	0.12
Schizophrenia spectrum	4 (4.2)	3 (18.8)	1 (1.3)	0.014
Autism spectrum	3 (3.2)	1 (6.3)	2 (2.5)	0.20
Eating disorder	2 (2.1)	0 (0)	2 (2.5)	0.69
Antipsychotic treatment (n, %)				
Any antipsychotic	39 (40.6)	7 (43.8)	32 (40.8)	0.78
Risperidone	14 (14.6)	2 (12.5)	12 (15.0)	0.80
Quetiapine	9 (9.4)	2 (12.5)	7 (8.8)	0.64
Aripiprazole	8 (8.3)	1 (6.3)	7 (8.8)	0.74
Olanzapine	5 (5.2)	1 (6.3)	4 (5.0)	0.84
Ziprasidone	3 (3.1)	1 (6.3)	2 (2.5)	0.423
First-generation antipsychotic	3 (3.2)	0 (0.0)	3 (3.8)	0.79
Chlorpromazine equivalent (mg/day)	167 $\pm$ 204	166 $\pm$ 110	168 $\pm$ 218	0.98
Nonantipsychotic treatment (n, %)				
Anxiolytics/hypnotics (n, %)	8 (8.3%)	4 (25%)	4 (5%)	0.025
Antidepressants (n, %)	32 (33.3%)	3 (18.8%)	29 (36.3%)	0.18
Mood stabilizers (n, %)	27 (28.1%)	6 (37.5%)	21 (26.3%)	0.36
Stimulants (n, %)	11 (11.5%)	2 (12.5%)	9 (11.3%)	0.89

QTc = rate-corrected QT interval.

shown that screening EKG's before starting stimulants have an appropriate balance of benefit, risk and cost effectiveness for general use in identifying risk factors for sudden death" (Perrin et al. 2008). If confirmed in larger studies, our findings would suggest restricting screening ECG's in youth requiring antipsychotic treatment to those considered to be at higher risk on account of heart disease, obesity, and hypokalemia.

Disclosures

Dr. Correll has been a consultant to or has received honoraria from Actelion, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Glaxo Smith Kline, Hoffmann-La Roche, Lundbeck, Medicure, OrthoMcNeill-Janssen, Otsuka, Pfizer, Schering-Plough, Supernus, Takeda, and Vanda. Dr. Kane has been a consultant to Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, and Otsuka, and has received honoraria from Abbott, Bristol-Myers Squibb, and Janssen. Dr. Manu has served on the speaker/advisory boards of Eli Lilly, Pfizer, and Bristol-Myers Squibb and on the speaker bureau for Forest Laboratories.

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References

- Blair J, Scahill L, State M, Martin A: Electrocardiographic changes in children and adolescents treated with ziprasidone: A prospective study. *J Am Acad Child Adolesc Psychiatry* 44:75–79, 2005.
- Correll CU, Manu P, Olshansky V, Napolitano B, Kane JM, Malhotra AK: Cardiometabolic risk of second generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 302:1765–1773, 2009.
- Gajewski KK, Saul JP: Sudden cardiac death in children and adolescents (excluding sudden infant death syndrome). *Ann Pediatr Cardiol* 3:107–112, 2010.
- Güven A, Özgen T, Gungör O, Aydın M, Baysal K: Association between the corrected QT interval and carotid artery intima-media

- thickness in obese children. *J Clin Res Pediatr Endocrinol* 2:21–27, 2010.
- Haase HJ: Zur Dosierung von Neuroleptika. Ein Leitfaden für Klinik und Praxis unter Berücksichtigung psychotisch Kranker. Erlangen: Perimed Fachbuch-Verlagsbuchhandlung; 1983.
- Haddad PM, Anderson IM: Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 62:1649–1671, 2002.
- Lubart E, Segal R, Yearovoi A, Fridenson A, Baumoebl Y, Leibovitz A: QT interval disturbances in hospitalized elderly. *Isr Med Assoc J* 11:147–150, 2009.
- Moss AJ: Measurement of the QT interval and the risk associated with QTc interval prolongation: A review. *Am J Cardiol* 72:23B–25B, 1993.
- Nigro G, Russo V, Di Salvo G, De Crescenzo I, Rago A, Perrone L, Golino P, Russo MG, Calabro R: Increased heterogeneity of ventricular repolarization in obese nonhypertensive children. *Pacing Clin Electrophysiol* 33:1533–1539, 2010.
- Perrin JM, Friedman RA, Knilans TK; Black Box Working Group: Cardiovascular monitoring and stimulant drugs for attention deficit/hyperactivity disorder. *Pediatrics* 122:451–453, 2008.
- Rautarhaju PM, Zhou SH, Wong S, Calhoun HP, Berenson GS, Prineas R, Davignon A: Sex differences in the evolution of the electrocardiographic QT interval with age. *Can J Cardiol* 8:690–695, 1999.
- Varley CK, McClellan J: Implications of marked weight gain associated with atypical antipsychotic medications in children and adolescents. *JAMA* 302:1811–1812, 2009.
- Vieweg WV: Mechanisms and risks of electrocardiographic QT interval prolongation when using antipsychotic drugs. *J Clin Psychiatry* 63 Suppl 9:18–24, 2002.
- Vieweg WV, Wood MA, Fernandez A, Beatty-Brooks M, Hasnain M, Pandurangi AK: Proarrhythmic risk with antipsychotic and antidepressant drugs: Implications in the elderly. *Drugs Aging* 26:997–1012, 2009.
- Wilens TE, Biederman J, Baldessarini RJ, Geller B, Scheifer D, Spencer TJ, Birmaher B, Goldblatt A: Cardiovascular effects of therapeutic doses of tricyclic antidepressants in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 35:1491–1501, 1996.
- Woods SW: Chlorpromazine equivalent doses for newer atypical antipsychotics. *J Clin Psychiatry* 64:663–667, 2003.

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