Evaluation of QTc Interval Effects of Antipsychotic Medications for Intensive Care Unit Delirium in Pediatric Patients

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OBJECTIVE Intensive care unit delirium is an increasingly recognized problem in pediatric patients. Controversy exists regarding the safety and efficacy of antipsychotic medications for this indication. The objective of this study was to determine the incidence of and risk factors for QTc interval prolongation in pediatric patients treated with antipsychotics for ICU delirium.

METHODS Retrospective chart review of pediatric patients admitted to the pediatric ICU or pediatric cardiac ICU and diagnosed with ICU delirium between October 1, 2014, and October 31, 2015. Patients were included if they received at least 1 dose of an antipsychotic for the treatment of delirium after a positive screen using the Cornell Assessment of Pediatric Delirium scoring tool.

RESULTS For the 26 patients included, the median change in QTc interval on treatment was -4 msec. Two patients (8%) had QTc interval prolongation while on antipsychotic therapy. No risk factors were identified in these 2 patients that put them at increased risk for QTc interval prolongation.

CONCLUSIONS The incidence of QTc interval prolongation in pediatric patients who were treated with antipsychotics for ICU delirium was low. There is need for future research to determine which pediatric patients are at risk for QTc interval prolongation when antipsychotic medications are used for the treatment of ICU delirium.

ABBREVIATIONS CAPD, Cornell Assessment of Pediatric Delirium; ECG, electrocardiogram; ICU, intensive care unit; PCICU, pediatric cardiac intensive care unit; PICU, pediatric intensive care unit

KEYWORDS antipsychotics; intensive care unit delirium; QTc interval prolongation; pediatric delirium

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Introduction

Intensive care unit (ICU) delirium occurs in 45% to 87% of critically ill adult patients and is associated with increased mortality, cost, hospital length of stay, and long-term cognitive impairment.¹ In the last decade, similar research has emerged regarding the incidence and severity of ICU delirium in children.^{2,3} Current research suggests between 20% and 40% of all pediatric ICU patients experience delirium during their ICU stays.^{2,4} ICU delirium in pediatric patients has also been associated with increased duration of mechanical ventilation, increased hospital length of stay, and increased costs.⁵ Multiple screening tools have been validated to assess for pediatric ICU delirium, including the Cornell Assessment of Pediatric Delirium (CAPD), Pediatric Confusion Assessment Method for the ICU, and the Preschool Confusion Assessment Method for the ICU, leading to increased recognition.⁶⁻⁸

Given the potential consequences of delirium, treatment may be necessary to shorten the duration of delirium.⁹⁻¹¹ Based on practice in adults and successful treatment of other psychiatric diseases, antipsychotics,

including both typicals and atypicals, are increasingly used off-label for treatment of ICU delirium in children.¹²⁻¹⁴ It remains unknown, however, whether this treatment is safe or effective. Use of antipsychotics in adults and other pediatric populations has been associated with QTc prolongation and may occur in up to 40% of these patients.¹⁵⁻¹⁸ QTc prolongation can deteriorate into a potentially fatal arrhythmia, Torsades de Pointes. In addition, critically ill children may be at particularly high risk for QTc prolongation and associated arrhythmia because they receive numerous medications, can have electrolyte disturbances, and can potentially have altered drug disposition and metabolism compared with adults.¹⁹ Given the limited pediatric data regarding the safety of antipsychotics for this indication in pediatrics, we aimed to determine the incidence of and risk factors for QTc interval prolongation in critically ill children administered antipsychotics for treatment of ICU delirium at an academic medical center.

Materials and Methods

This was a retrospective chart review of all pediatric

patients admitted to the pediatric intensive care unit (PICU) or pediatric cardiac intensive care unit (PCICU) at Duke Children's Hospital and Health Center, Durham, NC, between October 1, 2014, and October 31, 2015. We included all patients younger than 18 years of age who received at least 1 dose of an antipsychotic (risperidone, quetiapine, olanzapine, or haloperidol) for the treatment of delirium while admitted to the PICU or PCICU. Included patients must have had at least 1 ECG performed within 1 month prior to starting antipsychotics and 1 ECG while on antipsychotic therapy. Patients were excluded if they received antipsychotic therapy prior to ICU delirium diagnosis.

From the electronic health record, we recorded demographic information (i.e., age, gender, race), baseline and treatment QTc intervals, history of congenital heart disease or arrhythmias, hypokalemia or hypomagnesemia during antipsychotic therapy, duration of antipsychotic therapy, total daily dose of antipsychotic therapy, number of concomitant QTc interval prolonging medications received during antipsychotic therapy, method for determining delirium diagnosis, and delirium scores prior to and during antipsychotic therapy. We defined delirium as having a positive delirium screen using the CAPD (>9) or had a documented diagnosis of ICU delirium in their progress notes. The protocol at our institution was to screen for delirium using the CAPD score every 12 hours and follow delirium prevention protocols, including clustering of care, day and night regulation, and noise reduction, for all patients admitted to either ICU. If a patient had multiple ECGs during the admission within the month prior to initiation of antipsychotic therapy, we used the QTc interval on the ECG immediately prior to therapy as baseline. If multiple ECGs were obtained during therapy, the mean QTc interval was used as the on-therapy QTc interval to account for day-to-day variability in QTc intervals. We considered medications to potentially prolong the QTc interval if they were listed on the CredibleMeds website as having a conditional, possible, or known risk of causing torsades de pointes.²⁰ Normal for age QTc interval reference ranges were those reported by Rijnbeek et al²¹ in 2001. The pediatric cardiologist on service independently determined all QTc interval measurements, correcting QT intervals using the Bazett formula.²² Congenital heart conditions noted include hypoplastic left heart syndrome, transposition of the great arteries, Tetralogy of Fallot, and coarctation of the aorta. We considered a patient to have hypokalemia or hypomagnesemia if serum potassium was lower than 3.8 mmol/L or serum magnesium was lower than 1.9 mg/dL, respectively.

To determine whether there was a significant difference for all patients between baseline and on-therapy QTc interval, we performed a Wilcoxon signed rank test comparing the median difference between baseline QTc interval and the on-therapy QTc interval. We developed an ordinary linear regression model using

the difference between baseline and on-therapy QTc interval as the outcome. We used this model to determine which risk factors predisposed patients to elevated QTc-interval while receiving antipsychotics. Age, gender, race, history of arrhythmia or congenital heart disease, presence of abnormal serum electrolytes on therapy, number of concomitant QTc interval prolonging medications (0, 1, or 2+ concomitant medications), therapy duration, and total daily dose of medication were candidate variables considered for inclusion in the model. Variables that were not significant predictors after adjustment for other covariates (p value > 0.1) were removed in a backward selection process.

Results

We identified 37 patients admitted to the PICU or PCICU who were administered antipsychotic medications for the treatment of ICU delirium during our study period. We excluded 8 patients: 1 patient was missing a baseline ECG and 7 patients were lacking an ECG on therapy. Twenty-nine patients were included in the analysis (Table 1). The majority of the patients were Caucasian (17/26, 59%) and most patients received risperidone (25/29, 86%). Two (7%) patients received haloperidol and 1 (3%) patient each received quetiapine and olanzapine. The median baseline and on-treatment QTc intervals of the study patients were 434 msec (IQR, 417–445 msec) and 429 msec (IQR, 408–448 msec), respectively (Table 2). The median difference in QTc interval was –4 msec (IQR, –29 to 11 msec, $p = 0.86$). None of the evaluated risk factors were associated with change in QTc interval while on antipsychotic therapy. There were no documented arrhythmias for any patient. Two patients (7.7%) with normal baseline QTc interval experienced QTc interval prolongation on antipsychotic therapy. These 2 patients were 0.5 and 0.67 years of age and both received risperidone 0.03 and 0.08 mg/kg/day, respectively. They were on risperidone for 18 and 4 days and received 7 and 4 concomitant QTc-prolonging medications, respectively. Patient 1's QTc increased from a baseline of 434 to 451 while on treatment, and Patient 2's QTc increased from 376 to 450 while on treatment. Patient 1 had concomitant hypomagnesemia, hypocalcemia, and hypokalemia, whereas Patient 2 only had concomitant hypokalemia. The mean doses of risperidone, quetiapine, olanzapine, and haloperidol were 0.03, 0.04, 1.9, and 0.26 mg/kg/day, respectively. The median baseline CAPD score prior to treatment was 17 (IQR, 13.8–20) and the median on-therapy CAPD score was 11.7 (IQR, 8.2–15.5).

Discussion

Intensive care unit delirium treatment remains an evolving, complicated, and controversial subject. Limited data exist regarding the benefits or safety of antipsychotic medications in the treatment of ICU delirium in pediatric patients. In this small, retrospective study,

Table 1. Demographics and Baseline Data (N = 29)

Data	Result
Age, median (IQR), yr	0.7 (0.5–2)
Sex, n (%), male	15 (51.7)
Race, n (%)	
Caucasian	17 (58.6)
African American	6 (20.7)
Other	6 (20.7)
Antipsychotics, n (%)	
Risperidone	25 (86.2)
Haloperidol	2 (6.9)
Quetiapine	1 (3.4)
Olanzapine	1 (3.4)
History of congenital heart disease, n (%)	9 (31.0)
History of arrhythmia, n (%)	4 (13.8)
Duration of therapy, median (range), days	10 (2–53)
Number of concomitant QTc interval prolonging medications, median (range)	5 (2–12)
Hypokalemia, n (%)	27 (93.1)
Hypomagnesemia, n (%)	17 (58.6)
Normal QTc interval at baseline, n (%)	22 (75.9)

antipsychotic medications used for the treatment of pediatric ICU delirium did not increase QTc interval in the study population. There were, however, 2 patients with a normal baseline QTc interval who developed prolonged QTc intervals while on antipsychotic therapy.

The relatively small proportion of children in our study who developed QTc prolongation is consistent with data in adults. Recent literature suggests 10% of adult patients treated with antipsychotics for ICU delirium may experience QTc interval prolongation.²³ Joyce et al¹⁴ evaluated the QTc-prolonging effects of quetiapine used to treat pediatric ICU delirium in 50 children receiving an average daily dose 1.3 mg/kg/day. Among 16 children with ECGs within 7 days after quetiapine initiation, 3 had prolonged QTc intervals, with 2 cases resolving without any intervention and 1 requiring a reduction in quetiapine dose. However, none of these patients had QTc intervals assessed prior to quetiapine initiation; therefore, the extent of prolongation attributable to quetiapine is unknown. Among the 50 total children receiving therapy, none had clinically significant episodes of dysrhythmia.¹⁴

Most of the evidence for QTc interval prolongation in children treated with antipsychotics is during treatment for conditions other than delirium, including schizophrenia, aggression, autism, and attention-deficit/hyperactivity disorder.^{24,25} Palanca-Maresca et al²⁵ recently published a long-term follow-up study regarding QTc interval prolongation among children and adolescents treated with antipsychotic medications. Approximately 6% of patients treated with risperidone experienced

ECG abnormalities while on treatment. The median change from baseline in QTc interval was between 3 and 17 msec, depending on duration of treatment.²⁵ No patients experienced QTc intervals greater than 500 msec or any arrhythmias. In a meta-analysis of antipsychotic treatment in children and adolescents, the mean change in QTc interval was 1.92 and 1.68 msec with quetiapine and risperidone, respectively.²⁶

There were multiple limitations to our study. First, we conducted a retrospective review of a small number of pediatric patients at a single center. Second, the protocol implemented at our center recommended a baseline and weekly ECG to assess QTc interval, but this was not always followed, with several patients receiving ECG monitoring every day to every 10 days. We are currently developing an order panel to help facilitate compliance with QTc monitoring. Third, we did not examine drug-drug interactions that could have contributed to increased drug exposure and QTc prolongation. Fourth, although we examined QTc interval effects of antipsychotics in these patients, we did not evaluate other adverse effects, including extrapyramidal side effects. Additionally, we did not account for differences among various QTc prolonging medications and doses and simply counted the total number of these medications. Furthermore, the main medication used in our study was risperidone, thereby, limiting our ability to draw conclusions on other antipsychotics and compare our results to other studies using different antipsychotics, specifically quetiapine. Patients were included if

Table 2. Baseline QTc Intervals Compared With Antipsychotic Therapy QTc Intervals

Parameter	Median (IQR)
Baseline QTc interval, msec	434 (417–445)
QTc interval on antipsychotics, msec	429 (408–448)
Difference in QTc interval, msec	–4* (–29 to 11)

* p value = 0.086

they received only 1 dose of medication, so therefore, they may or may not have reached steady state in their dosing and may have experienced more significant adverse effects if continued for longer periods of time, although the shortest duration of treatment was 2 days. Finally, the CAPD score has not been validated to determine efficacy of antipsychotics when used for the treatment of ICU delirium in children. We did see a decrease in the CAPD scores on treatment, however, it is unknown the clinical significance of this decrease and should be interpreted with caution. However, our study is 1 of the first to examine a cohort of critically ill children receiving antipsychotics for the treatment of pediatric delirium, thereby contributing to the limited existing body of knowledge.

Conclusion

In this small, retrospective study, the use of antipsychotics was not associated with QTc prolongation when used to treat pediatric ICU delirium, although 2 patients on risperidone did develop QTc prolongation on treatment. Given the increasing recognition of delirium and increased off-labeled use of antipsychotics for the treatment of delirium in the critically ill population despite lack of efficacy data, additional study is warranted to ensure these medications are safe and effective for this clinical use, especially in children. Further study should include evaluation of extrapyramidal side effects and clinical efficacy in addition to evaluation of QTc prolongation and arrhythmia in pediatric patients.

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