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QTc Prolongation and Arrhythmia Development in the Treatment of ICU Delirium: An Investigation of Medication-Related Risk Factors

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Authors' contributions

This work was carried out in collaboration between all authors. Author AF performed the literature searches, designed the study, wrote the protocol, performed data collection, interpretation of the results and wrote the first draft of the manuscript. Authors DSE and JMB contributed to the study design, interpretation of the results and reviewed and edited all drafts of the manuscript. Author GP managed the analyses of the study. Author CVM developed the research question, provided oversight to all aspects of the study and was responsible for the final draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Antipsychotics are commonly used for ICU delirium, although there is limited data describing the risk of QTc prolongation with these therapies. This study aimed to evaluate the prevalence of and risk factors for QTc prolongation associated with antipsychotic agents for ICU delirium.
Study Design: A retrospective cohort study of patients with ICU delirium who received an antipsychotic agent.
Place and Duration of Study: The Ohio State University Wexner Medical Center Surgical and Medical ICUs, between January 1st, 2012 and January 1st, 2015.

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Methodology: QTc prolongation was defined as QTc >500 ms or >20% increase from baseline. The primary outcome was the prevalence of QTc prolongation. Secondary outcomes included risk factors for QTc prolongation, prevalence of Torsades de Pointes (TdP) or ventricular arrhythmias, ICU length of stay, length of delirium treatment, and all-cause ICU mortality.
Results: Two hundred and nine patients were included, with 27 (13%) patients developing QTc prolongation. In univariate analysis, patients with QTc prolongation had higher baseline QTc (median 453 vs. 442.5 ms) and increased use of concomitant antiarrhythmic (22.2 vs 8.2%) and antidepressant (11.1 vs 5.5%) agents. In multivariable logistic regression, medium [AOR 0.2; 95% CI 0.06-0.74; P=.02] and high [AOR 0.10; 95% CI 0.01-0.80; *P*=.03] antipsychotic agent dose intensity were associated with decreased risk of QTc prolongation. Three patients in the no QTc prolongation group developed a ventricular arrhythmia, but no episodes of TdP were observed in either group.
Conclusions: The rate of QTc prolongation in patients receiving antipsychotics for ICU delirium was relatively low and may not correlate with arrhythmia risk. While no clinically relevant risk factors were identified to predict risk of QTc prolongation in this population, the low rate of QTc prolongation and ventricular arrhythmias indicate that further research is needed to determine if frequent ECG monitoring is truly indicated in this population.

Keywords: Torsades de pointes; QT prolongation; drug-related side effects and adverse reactions; delirium; critical illness.

1. INTRODUCTION

Nearly 80-85% of sudden cardiac arrest cases are believed to be associated with ventricular arrhythmias [1]. Torsades de Pointes (TdP) is a unique form of ventricular tachycardia associated with prolongation of the corrected QT interval (QTc) with the potential to develop into life-threatening ventricular fibrillation [2]. A variety of risk factors for developing prolonged QTc exist in non-critically ill patients, including electrolyte abnormalities, myocardial ischemia, female gender, low body mass index (BMI), older age, renal or hepatic insufficiency, and certain medications [2,3]. A previous study reported a fairly low rate (2.6%) of QTc prolongation (>500 ms) among hospitalized medical patients [4]. Critically ill patients may be at a higher risk for developing prolonged QTc, given a greater likelihood of acquiring additional risk factors, such as medications with QTc prolonging potential, renal/hepatic insufficiency, and electrolyte abnormalities [5]. Pickham and colleagues observed a prevalence of QTc prolongation (> 500 ms) of 24% among critically ill patients, with independent predictors of prolongation including QTc prolonging medications, hypokalemia and elevated serum creatinine [6]. The most common non-cardiac QTc prolonging medication class used in the intensive care unit (ICU) is antipsychotics, and use of these agents is likely increasing due to increased recognition and pharmacologic management of ICU delirium [7].

Currently there is limited data to guide identification of patients at risk for QTc prolongation in the ICU. However, patients co-administered medications with QTc prolonging potential have been found to have higher mortality rates and longer ICU lengths of stay, indicating that increased ECG monitoring may be necessary [8]. To date, no studies have specifically evaluated QTc prolongation and development of malignant arrhythmias in ICU patients being treated for delirium with antipsychotics. However, more accurate identification of critically ill patients with delirium who are at high risk for QTc prolongation may allow for targeted ECG monitoring and more thoughtful medication therapy adjustments. Therefore, this study aimed to identify medication-related risk factors for QTc prolongation and progression to arrhythmia among ICU patients receiving pharmacologic treatment of ICU delirium.

2. METHODOLOGY

2.1 Study Design and Patient Population

A single-center, retrospective cohort study was conducted to identify variables associated with QTc prolongation among adult patients managed with antipsychotics for ICU delirium. The Ohio State University Institutional Review Board approved the study (Approval Number 2014H0410), and the requirement for consent was waived. All authors hereby declare that all experiments have been examined and approved

by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Adult patients (≥18 years old) who were treated for ICU delirium with a scheduled antipsychotic agent while admitted to the medical intensive care unit (MICU) or surgical intensive care units (SICU) between January 1st, 2012 and January 1st, 2015 were eligible for evaluation. Additional criteria for inclusion were availability of a baseline–ECG reading with QTc measurement prior to the initiation of ICU delirium treatment, at least one follow-up ECG reading with QTc measurement during ICU delirium treatment, and scheduled administration of at least one of the following antipsychotic agents for the treatment of ICU delirium: haloperidol, risperidone, quetiapine, olanzapine. ICU delirium was identified according to the Confusion Assessment Method for ICU patients (CAM-ICU), with at least two consecutive positive scores required to qualify for inclusion. Exclusion criteria consisted of ventricular pacing, bundle branch block, incarceration, pregnancy, patients on selected antipsychotics prior to admission to either the hospital or the ICU (haloperidol, risperidone, quetiapine, and olanzapine), and congenital long QT syndrome. If a patient qualifies for inclusion under multiple hospital encounters, only the first episode within the study time period was included.

For study purposes of the primary analysis, QTc prolongation was defined as QTc > 500 ms or > 20% increase in QTc from baseline QTc measurement. All available ECG readings with QTc measurement during treatment of ICU delirium were evaluated for QTc prolongation. This definition was derived based on the clinical significance of QTc >500 ms plus the probable clinical significance of a >20% increase in QTc even if ultimately the peak QTc was below 500 ms. Secondary analyses used alternative definitions based on the FDA categorization for QTc prolongation including >450 ms, >480 ms, >500 ms, > 30 ms increase from baseline and > 60 ms from baseline [9]. All ECG data was obtained using the GE MUSE ECG reader, which calculates QTc using Bazett's formula. All ECG measurements are interpreted and confirmed by a cardiologist.

2.2 Study Outcomes and Data Collection

The primary outcome was to determine the prevalence of QTc prolongation and subsequently identify medication-related risk factors associated with QTc prolongation in the ICU delirium population. Secondary outcomes included prevalence of TdP or ventricular arrhythmias, ICU length of stay, length of delirium treatment, and all-cause ICU mortality. Data was collected retrospectively from the electronic medical record and included baseline patient characteristics, potential delirium treatment related risk factors for QTc prolongation (antipsychotic medication administered, dose, and route of administration), and previously published risk factors for QTc prolongation as identified by the American Heart Association and American College of Cardiology Foundation (gender, age, electrolyte abnormalities, treatment with diuretics, concomitant QTc prolonging medications, hepatic dysfunction, underlying cardiac comorbidities, and serum creatinine) [10]. Dose intensity of the antipsychotic agent used for ICU delirium treatment was based on the total daily dose at the time of longest documented QTc as follows: low (quetiapine 50 mg or less, risperidone 1 mg or less, olanzapine 5 mg or less, haloperidol 5 mg or less), medium (quetiapine >50 mg and <150 mg, risperidone >1 mg and <3 mg, olanzapine >5 mg and <20 mg, haloperidol > 5mg and <20 mg) and high (quetiapine 150 mg and higher, risperidone 3mg and higher, olanzapine 20mg and higher, haloperidol 20 mg and higher). These thresholds were chosen based on recommended dosing ranges in the institutional ICU delirium guideline. Electrolyte abnormalities were defined as follows: potassium <3.4 mEq/L, magnesium < 1.6 mg/dL, and ionized calcium <4.6 mg/dL based on normal reference values set by the institutional laboratory. Medications considered to be QTc prolonging were determined using the Arizona Center for Education and Research on Therapeutic classification system [11]. Medications classified as having "Known risk for TdP" were included for the purposes of this study and classified by category as outlined in Table 1. Patients were classified as receiving an additional concomitant antipsychotic agent if they received at least one of the antipsychotic agents listed in Table 1 in addition to their primary antipsychotic for ICU delirium treatment.

Patients were considered to have hepatic dysfunction if it was documented in their active medical problem list or past medical history. Cardiac comorbidities were also based on documentation in the active medical problem list or past medical history and included congestive heart failure, previous myocardial infarction, sinus bradycardia, and heart block.

Table 1. QTc prolonging medications with known risk for Torsades de Pointes

Antiarrhythmics	Antibiotic	Antipsychotic	Antidepressant	Miscellaneous
Amiodarone	Azithromycin	Chlorpromazine	Citalopram	Anagrelide
Disopyramide	Ciprofloxacin	Droperidol	Escitalopram	Arsenic Trioxide
Dofetilide	Erythromycin	Pimozide		Chloroquine
Dronedarone	Fluconazole	Thioridazine		Halofantrine
Flecainide	Levofloxacin	Haloperidol*		Methadone
Ibutilide	Moxifloxacin			Ondansetron
Quinidine	Pentamidine			Propofol
Sotalol				Vandetanib

**as needed use in addition to a scheduled qualifying antipsychotic*

2.3 Statistical Analysis

Patient demographics and clinical characteristics are summarized where categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviations (SD) or median and the interquartile range (IQR) depending on the distribution. Logistic regression was used to determine which patient demographics and clinical characteristics are independently associated with QTc prolongation. Covariates evaluated included age, gender, ICU location (medical vs. surgical), history of CHF, MI, sinus bradycardia, heart block, or hepatic dysfunction, choice of antipsychotic agent for ICU delirium treatment (quetiapine, risperidone, olanzapine, haloperidol), dose intensity (low, medium, high), duration of antipsychotic exposure in days, presence of electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), serum creatinine, concomitant administration of a diuretic, and presence of an concomitant agent with known QTc prolongation risk based on the categories antiarrhythmic, antidepressant, antipsychotic, antibiotic, and miscellaneous. A covariate is only entered into the model if it is a confounder or an effect modifier of the relationship between delirium treatment agent and QTc prolongation. A confounder is defined if the QTc prolongation odds ratio changes by 10% in either direction when the covariate is entered into the model compared to when it was not in the model. An effect modifier is defined when the covariate has a statistically significant interaction with the risk factor (interaction p-value ≤ 0.05). The multiple *p*-values produced in the study were adjusted using the Holms procedure to control the overall type I error at 0.05 due to the multiple comparisons. All analyses were run using Stata 13.1, StataCorp, College Station, Texas.

3. RESULTS

During the study period, 1153 patients were administered one or more of the selected antipsychotic agents while admitted to the MICU or SICU and were reviewed for study inclusion. Nine hundred forty four patients were excluded, with primary reasons for exclusion consisting of absence of repeat ECG after initiation of delirium treatment, as needed use only of delirium medication, or use of delirium treatment prior to admission (Fig. 1).

Overall, 209 patients were included for analysis, with 27 (13%) patients demonstrating QTc prolongation during their delirium treatment course using the study definitions for QTc prolongation (>500 ms or >20% increase from baseline). Twenty-one patients met criteria with a QTc >500 ms, while 6 met criteria with a >20% increase from baseline QTc. Fig. 2 depicts the prevalence of QTc prolongation using the various definitions; the rate ranged from 10% to 56% with the highest prevalence associated with QTc>450 ms and the lowest with using a change from baseline of >60 ms.

The majority of patients included were male, in their 6th decade of life, and admitted to the MICU (Table 2). Patients in the QTc prolongation group had significantly longer baseline QTc values compared to those in the no QTc prolongation group. The prevalence of QTc prolonging home medications was similar and generally fairly low in both groups, although there was a trend towards higher use of antiarrhythmics at home in the QTc prolongation group. There was a trend towards greater incidence of cardiac comorbidities in the QTc prolongation group, including past medical history of heart failure and myocardial infarction.

For analysis of data obtained during the period of active delirium treatment for each patient, values associated with the longest QTc reading were evaluated (Table 3). The median maximum QTc for the non-prolongation group was 450 ms compared to 510 ms in the QTc prolongation group. For delirium treatment, patients were most frequently on quetiapine or risperidone in both groups at the time of longest documented QTc value. No patients in either group received scheduled dosing of two or more of the primary antipsychotic agents concomitantly although a larger proportion (42.6% of cohort) received an additional antipsychotic (Table 3). There was a greater proportion of patients with hypokalemia in the QTc prolongation group compared to the non-QTc prolongation group. With regards to concomitant QTc prolonging medications, more patients in the QTc prolongation group received antiarrhythmic and antidepressant agents compared to the non-QTc prolongation group (Table 3).

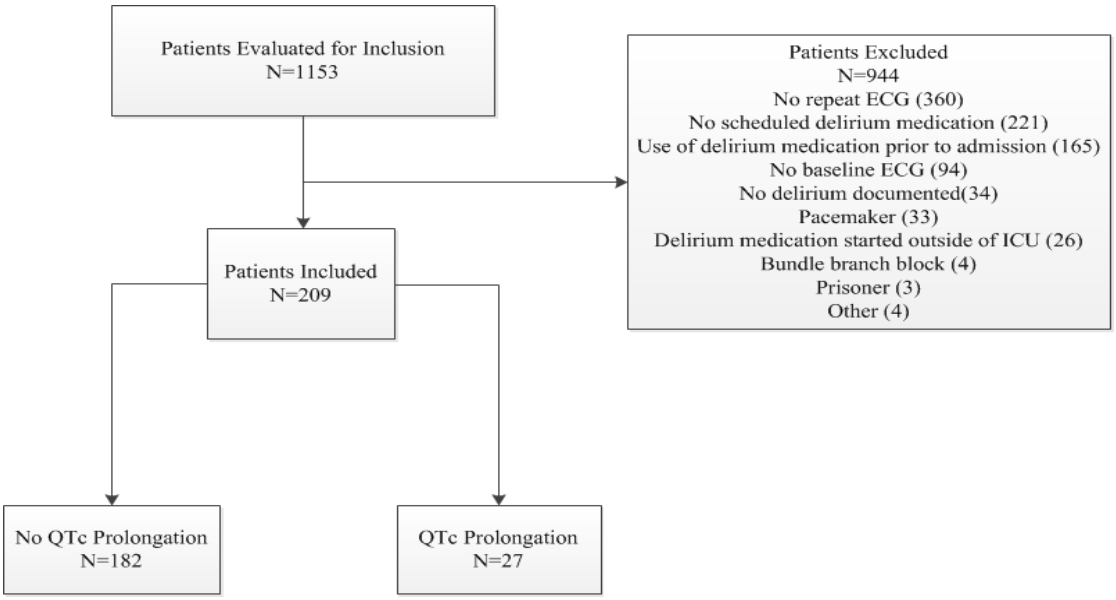

Fig. 1. Flow diagram of included and excluded patients

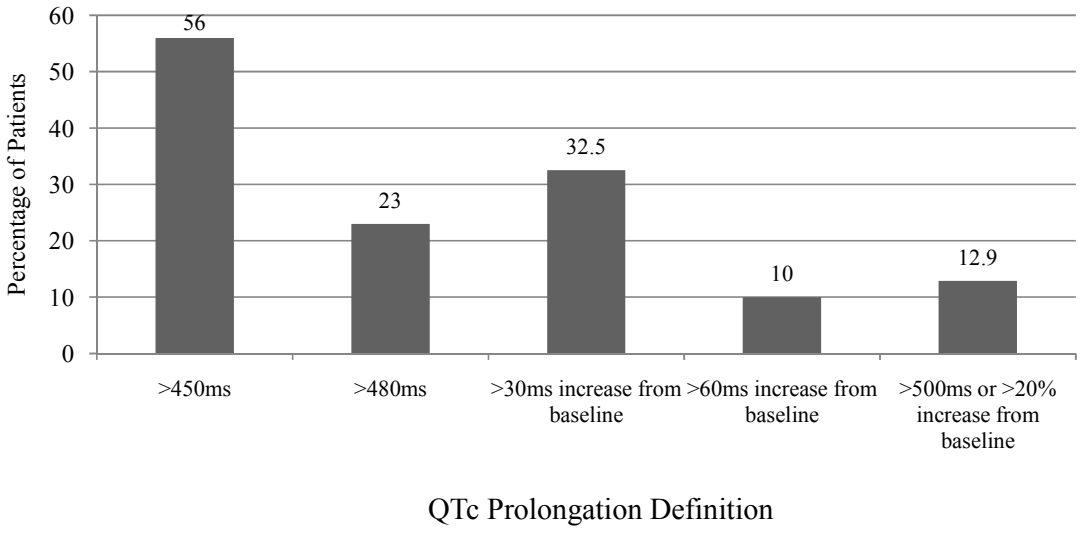

Fig. 2. Prevalence of QTc prolongation based on definition (n=209)

Table 2. Baseline characteristics compared between patients with no QTc prolongation and patients with QTc prolongation

	Entire Cohort N=209	No QTc Prolongation N=182	QTc Prolongation N=27
Age, years (mean ± SD)	61 ± 14.5	61.1 ± 14.3	63.9 ± 16.2
Male sex, n(%)	134 (64.6)	115 (63.2)	20 (74.1)
Hospital unit, n(%)			
MICU	128 (61.2)	109 (59.9)	19 (70.4)
SICU	81 (38.8)	73 (40.1)	8 (29.6)
Serum creatinine (mean ± SD)	1.5 ± 1.4	1.5 ± 1.4	1.3 ± 0.8
Hepatic dysfunction, n(%)	15 (7.2)	13 (7.1)	2 (7.4)
Baseline QTc, ms (median [IQR])	443 [424-470]	442.5 [425-467]	453 [419.5-486]
Cardiac comorbidities, n (%)			
Heart failure	23 (11)	18 (9.9)	5 (18.5)
Myocardial infarction	35 (16.7)	28 (15.4)	7 (25.9)
QTc prolonging home medications, n(%)			
Antiarrhythmics	4 (1.9)	2 (1.1)	2 (7.4)
Antidepressants	14 (6.7)	12 (6.6)	2 (7.4)
Antipsychotics	2 (0.9)	2 (1.1)	0 (0)
Antibiotics	5 (2.4)	5 (2.7)	0 (0)
Miscellaneous	9 (4.3)	9 (4.9)	0 (0)
Diuretic home medication, n (%)	69 (33)	59 (32.4)	10 (37)

MICU, Medical Intensive Care Unit; SICU, Surgical Intensive Care Unit

Table 3. Variables associated with longest QTc value during delirium treatment compared between patients with no QTc prolongation and patients with QTc prolongation

	Entire Cohort N=209	No QTc Prolongation N=182	QTc Prolongation N=27
Maximum QTc, ms (median [IQR])	456 [435-478]	450 [432.25-469]	510 [501.5-528]
Delirium treatment medication, n (%)			
Quetiapine	94 (45)	83 (45.6)	11 (40.7)
Risperidone	100 (47.8)	86 (47.3)	14 (51.9)
Haloperidol	10 (4.8)	9 (4.9)	1 (3.7)
Olanzapine	5 (2.4)	4 (2.2)	1 (3.7)
Electrolyte abnormality, n (%)			
Potassium <3.4 mEq/L	8 (3.8)	4 (2.2)	4 (18.8)
Magnesium <1.6 mg/dL	7 (3.3)	7 (3.8)	0 (0)
Ionized Calcium <4.6 mg/dL	61 (29.2)	52 (28.6)	9 (33.3)
QTc prolonging medications, n (%)			
Additional antipsychotics*	89 (42.6)	76 (41.8)	13 (48.1)
Antiarrhythmics	21 (10)	15 (8.2)	6 (22.2)
Antibiotics	28 (13.4)	27 (14.8)	1 (3.7)
Antidepressants	13 (6.2)	10 (5.5)	3 (11.1)
Miscellaneous	18 (8.6)	17 (9.3)	1 (3.7)
Diuretic, n (%)	55 (26.3)	50 (27.6)	5 (18.5)

**Antipsychotic agent in addition to the primary antipsychotic for ICU delirium (i.e. scheduled haloperidol, risperidone, quetiapine, or olanzapine. The additional antipsychotic could include. chlorpromazine, droperidol, pimozide, thioridazine or as needed haloperidol*

Table 4. Clinical outcomes compared between patients with no QTc prolongation and patients with QTc prolongation

	Entire Cohort N=209	No QTc Prolongation N=182	QTc Prolongation N=27
Ventricular arrhythmia*, n (%)	3 (1.4)	3 (1.6)	0 (0)
All-cause mortality, n (%)	60 (28.7)	49 (26.9)	11 (40.7)
ICU length of stay, days (median [IQR])	16 [10-24]	15 [10-23]	17 [12-27]
Delirium treatment duration, days (median [IQR])	8.5 [5-13]	9 [5-13]	6 [4-10]

**No Torsades de Pointes was observed*

ICU length of stay was similar between groups but all-cause ICU mortality was higher in the QTc prolongation group (OR 1.87, 95% Confidence Interval 0.81-4.3, *P* = .14) although this did not reach statistical significance (Table 4). Three patients in the no QTc prolongation group experienced any ventricular arrhythmia, and no episodes of TdP were documented for any patients in either study population.

Covariates evaluated for possible inclusion in the logistic regression analysis included age, gender, ICU location (medical vs. surgical), history of CHF, MI, sinus bradycardia, heart block, or hepatic dysfunction, choice of antipsychotic agent for ICU delirium treatment (quetiapine, risperidone, olanzapine, haloperidol), dose intensity (low, medium, high), duration of antipsychotic exposure in days, presence of electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), serum creatinine, concomitant administration of a diuretic, and presence of an concomitant agent with known QTc prolongation risk based on the categories antiarrhythmic, antidepressant, antipsychotic, antibiotic, and miscellaneous. Three covariates were found to confound the relationship between delirium treatment and QTc prolongation by at least 10% and were therefore included in the multivariable anlaysis: concomitant QTc prolonging antibiotics, concomitant diuretic use, and dose intensity (low, medium, or high) of the antipsychotic used of ICU delirium treatment. After adjustment for these variables, only dose intensity was significantly associated with QTc prolongation where both medium (*P*=.02) and high (*P*=.03) dose intensity were associated with decreased odds of QTc prolongation (Table 5). Of note, none of the variables included in the multivariable analysis were found to be statistically associated with QTc prolongation.

4. DISCUSSION

This study sought to identify any medication-related risk factors that may be associated with QTc prolongation and development of cardiac arrhythmias in the ICU delirium population. QTc

Table 5. Multivariable logistic regression model for risk factors for QTc prolongation

Medication-Related Risk Factor*	OR	95% CI		P-value
Delirium treatment				
Haloperidol	1.19	0.12	11.58	.88
Risperidone (referent group)	1.00			
Quetiapine	0.88	0.36	2.15	.78
Olanzapine	2.90	0.23	36.34	.41
Concomitant QTc prolonging antibiotics	0.22	0.03	1.80	.16
Concomitant diuretics	0.61	0.20	1.79	.37
Dose intensity of antipsychotic agent				
Low (referent group)	1.00			
Medium	0.21	0.06	0.74	.02
High	0.10	0.01	0.80	.03

**The following covariates were evaluated but did not meet criteria for inclusion in the logistic regression analysis: age, gender, ICU location (medical vs. surgical), history of CHF, MI, sinus bradycardia, heart block, or hepatic dysfunction, duration of antipsychotic exposure in days, presence of electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), serum creatinine, and concomitant QTc prolonging agents in the antiarrhythmic, antidepressant, antipsychotic, and miscellaneous categories*

prolongation was observed in 13% of patients while on delirium treatment. Patients with QTc prolongation were found to have a higher baseline QTc prior to delirium treatment initiation, as well as a higher incidence of concomitant antiarrhythmic and antidepressant medication use. To our knowledge, this is the first study to investigate QTc prolongation and associated medication risk factors in this patient population.

A concerning adverse effect associated with agents used to manage delirium in the ICU is the propensity to cause QTc prolongation, which increases the risk for developing TdP. A study evaluating adverse drug reactions associated with antipsychotic agents used for treatment of delirium found that 50% of all adverse reactions consisted of QTc prolongation [12]. While QTc prolongation may be prevalent, the exact incidence of TdP is largely unknown but is estimated to be very low. This is consistent with the results of the current study, with no patients developing TdP and only patients who did not develop QTc prolongation presented with any ventricular arrhythmia. Despite this low risk of TdP, clinicians are faced with the challenge of balancing the risk versus benefit of using QTc prolonging agents and the need for ongoing QTc monitoring. The current study suggests that patients with higher baseline QTc are potentially more likely to develop QTc prolongation, as are those with concomitant antiarrhythmic and antidepressant use. However, the only independent risk factor for QTc prolongation identified in the logistic regression model was lower dose intensity. Most likely this represents clinician hesitation to increase doses as the QTc begins to lengthen rather than a protective nature of higher doses. As the incidence of TdP was zero regardless of QTc in the current study, further research is needed to determine whether ongoing QTc monitoring is necessary in this population.

This study did reveal that patients with delirium who developed prolonged QTc may have worse outcomes independent of ventricular arrhythmias. The higher mortality among patients with QTc prolongation observed in the current study is consistent with findings from a study conducted by Freeman et al., which observed increases in both ICU length of stay and mortality with the use of multiple QTc prolonging agents [8]. Freeman et al. utilized a large ICU database to identify patients who were on QTc prolonging agents and analyzed the variability between patients on multiple QTc prolonging agents compared to the use of a single agent only. ECGs and QTc values were not available through the database. Our study similarly compared patients who received one or multiple QTc prolonging agents, but has the added advantage of including QTc values to further justify our outcomes. A possible explanation of these findings is that QTc prolongation may be associated with a patient population burdened by several comorbidities, naturally putting them at an inherently increased risk for complications and mortality during hospitalization independent of QTc prolongation.

The study has the limitations of being a retrospective and single-center study which can lead to restricted external applicability. The relatively small sample size with low rate of QTc prolongation limited the ability to perform a robust logistic regression model to identify independent factors associated with QTc prolongation. Use of Bazett formula for QTc estimation is known to have inherent risk for overestimation of the QTc, particularly with higher heart rates [13,14]. Therefore, there is a risk that the actual incidence of QTc prolongation is actually lower than reported here. In addition, for some patients, the baseline QTc value was the most prolonged, and subsequent measurements were shorter during delirium treatment. This is likely a reflection of the natural variation in QTc a patient may have, as well as situations where other temporary factors such as electrolyte abnormalities and use of other QTc prolonging medications may have been present. Data regarding dosing of concurrent QTc prolonging medications was not collected, which may limit the accuracy of evaluation of the role of these agents in risk of QTc prolongation in this population. Finally, based on the institutional guideline, risperidone and quetiapine are the preferred agents for delirium treatment. Therefore, application of these results to other agents such as ziprasidone, olanzapine and haloperidol is limited.

5. CONCLUSIONS

Frequency of QTc prolongation in patients receiving treatment for ICU delirium ranged from

10-56% depending on the definition use. However, malignant arrhythmias were not observed in any patient with QTc prolongation. While no clinically useful risk factors were identified for QTc prolongation, these results suggest that less ECG monitoring may be required than initially believed when using medications to treat ICU delirium, but further prospective investigation is warranted.

CONSENT AND ETHICAL APPROVAL

The Ohio State University Institutional Review Board approved the study (Approval Number 2014H0410), and the requirement for consent was waived. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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