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Increasing Risk Awareness for Torsades De Pointes: Evaluating QTc-Prolonging Medication use and ECG Monitoring in Hospitalized Patients

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Abstract

Purpose: The objectives of this study were to describe the prevalence of QTc-prolonging medication exposures among hospitalized patients and examine the association between QTc-prolonging medication exposure and new onset QTc-prolongation.

Methods: A retrospective cohort study was conducted among a convenience sample of patients hospitalized at Upstate University Hospital during a 6 month time period. Data including patient demographics, medication exposures, and ECG results were collected. Patients with a diagnosis of bundle branch block were excluded. Medications were categorized according to three risk groups for Torsades de Pointes: risk, conditional risk, and possible risk. An abnormal QTc interval was defined as >430 for men and >450 for women. Data were analyzed using SPSS statistical software.

Results: One hundred fifty patients were included. Mean age was 62 years (SD, 11.9), 80 patients (53.3%) were female, and the majority of patients were Caucasian (46.3%) or African American (38.3%). Ninety seven (64.7%) patients were prescribed medication associated with some risk for QTc prolongation, including 47 patients (31.3%) who were concurrently prescribed 2 or more QTc-prolonging medications. An EKG was performed in 112 (74.7%) patients and 76 (50.7%) had an abnormal QTc interval. Most abnormal QTc intervals were found upon admission with 9 patients experiencing new onset QTc prolongation during hospitalization. No significant association was found between QTc medication exposure and new onset QTc prolongation.

Conclusion: Hospitalized patients are at high risk for single and multiple QTc medication exposures. Although a substantial number of patients had an abnormal QTc interval, most were discovered upon admission and few experienced new onset QTc prolongation. A significant association between medication exposure and new onset QTc prolongation was not detected in this study.

Keywords: QTc-prolonging medications; Electrocardiogram

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Introduction

QTc interval prolongation, either congenital or acquired, has been associated with an increased risk for Torsades de pointes (TdP) and subsequent morbidity and mortality [1]. There are several risk factors for acquired QTc interval prolongation including electrolyte imbalances, bradycardia, structural heart disease, genetic susceptibility, and starvation [2-4]. Another common risk factor is drug therapy. Certain medications can directly cause QTc prolongation and have been associated with Torsades de points and sudden cardiac death. Furthermore, the use of medication that slow the metabolism of other drugs associated with QTc prolongation can also increase these cardiac risks [1,2,5].

Hospitalized patients may be at heightened risk for TdPdue to several factors. New medications with QTc prolongation risks or drug interaction risks may be administered to patients when hospitalized. Electrolyte disturbances commonly occur in hospitalized patients who are suffering from an acute illness. Also, these patients may have acute onset conditions including heart disease, renal or hepatic dysfunction, or bradycardia that may place them in a proarrhythmic state [1]. Close electrocardiogram (ECG) monitoring of these patients is possible due to their physical location within the hospital. The potential for developing TdP may be anticipated and discontinuation of

Table 1: Baseline Characteristics (N=150).

Characteristics	Value
Mean age in years (SD)	62(11.9)
Female Sex (%)	80(50.3)
Race (%) Caucasian African American Other	 69 46.3) 57 (38.3) 24 (16)
Median number of prescribed medications (interquartile range)	13 (9-18)
Admitting Diagnosis (%) Cardiovascular related Infectious Disease related Surgical COPD/Respiratory related Other	 31 (20.8) 32 (21.5) 18 (12) 17 (11.3) 52 (34.4)

the offending drug or appropriate alternative treatment options can be instituted.

There are currently few epidemiologic data to illustrate the prevalence of QT-prolonging drug exposures among hospitalized patients and the associated utilization of ECG monitoring. The limited data that we do have is derived from drug safety studies, patients with subarachnoid hemorrhage and alcoholic liver disease, and in otherwise healthy individuals [2]. The American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF) recently released a scientific statement intended to increase clinician awareness concerning drug-induced Torsades de pointes (TdP) among hospitalized patients [1]. Considerations for ECG monitoring were provided for patients treated with medications associated with QT prolongation. In the event that a drug-induced TdP event is suspected, the AHA/ACCF statement suggests discontinuing the offending agent, replacing potassium, administering magnesium, temporary pacing where clinically appropriate, and transferring the patient to a unit with the highest level of ECG monitoring [1].

The objectives of this study were to: (1) identify the prevalence of QT-prolonging medication exposures in hospitalized patients, (2) evaluate the use of ECG testing in patients using QT-prolonging medications and (3) ascertain the association been QT-prolonging medication exposure and QT interval among patients with available ECG data.

Materials and Methods

Study site and Population

A retrospective cohort study was conducted among hospitalized patients at a 472-bed Level 1 Trauma Center in Upstate New York. The study was granted exempt status by the Institutional Review Board (IRB). A convenience sample of 150 patients hospitalized during a six month time period from March 2012 to August 2012 was selected and medical records were retrospectively reviewed.

Data collection

Data collection included patient demographics, reason for admission, select co-morbid conditions, the presence of known risk factors for QT-prolongation, prescribed medications during hospitalization, and available ECG results. QT-prolonging medications were defined as medications present on the Arizona Credible-Meds QT drug list [6]. Prescribed medications were categorized according to their risk for QT-prolongation (risk, possible risk, and conditional risk of TdP) [7,8]. Each of these categories is defined according to the following criteria. Risk: medications have substantial evidence that

Table 2: Characteristics of QTc Medication Exposures and ECG Results.

Characteristic	Value
Patients with QTc prolonging medication exposure (%)	97 (64.7)
Patients with QTc medication exposure categorized by QTc medication risk group: 1. Risk 2. Conditional Risk 3. Possible Risk	 27 (18%) 27 (18%) 50 (30.3%)
Patients with 2 or more QTc prolonging medications prescribed concurrently	47 (31.3%)
Number of QTc prolonging medications used concurrently per patient 0 1 2 3 4 5	 53 (35.5%) 50 (33.3%) 28 (18.7%) 13 (8.7%) 4 (2.7%) 2 (1.3%)
Patients who had an ECG upon admission	112 (74.7%)
Patients who had a follow up ECG during hospitalization (%)	28 (17.3)
Patients with borderline/abnormal QTc upon admission	76 (50.7%)
Patients with new onset borderline/abnormal QTc prolongation	10 (6.7%)

supports the conclusion that these drugs prolong QT intervals and have a risk of TdP when used as directed in labeling. Possible risk: medications possess substantial evidence that supports the conclusion that these drugs can cause QT prolongation but there is insufficient evidence that the drugs, when used as directed in labeling, have a risk of causing TdP. Conditional risk: medications possess substantial evidence that supports the conclusion that these drugs prolong QT and have a risk of developing TdP but only under certain known conditions. Patients were also evaluated for pharmacodynamic QT interactions. A pharmacodynamic QTc interaction was defined as the concurrent use of two or more QTc-prolonging medications.

All ECG tests were recorded and analyzed for QTc prolongation. Patients diagnosed with bundle branch block were excluded from this latter part of the study since this condition is independently associated with QTc prolongation. QTc prolongation was defined according to the UK Committee for Proprietary Medicinal Products [7]. QTc interval was categorized as normal, borderline and prolonged [7]. Abnormal QTc interval was defined as a QTc interval that was borderline or prolonged. For men this was a QTc interval >430msec and for women a QTc interval > 450 msec. New onset QTc prolongation could only be considered in those patients who had a normal QTc interval measured during their hospitalization followed by an abnormal QTc interval.

Statistical analysis

Data were entered into SPSS statistical software and Student-t tests and chi-squared/Fisher's exact tests were used to compare interval and categorical data, respectively. Significance was associated with a p-value less than 0.05.

Results

In total, 150 patients were included in the study. Patient characteristics are represented in (Table 1). The characteristics of QTc prolonging medication exposures and ECG results are represented in (Table 2). Ninety-seven (64.7%) patients were prescribed medication associated with some risk for QTc prolongation. The majority of these medication exposures were to medications categorized as

Table 3: ECG Performance based upon QTc medication exposure.

Patient Characteristic	Baseline ECG Number (%)	Follow-up ECG Number (%)
Overall Patients (N=150)	112 (74.4%)	28 (17.3%)
Pts using ≥1 QTc medication (N=97)	75 (77.3%)	21 (21.6%)
Pts using ≥2 QTc medications (N=47)	38 (80.9%)	16 (34%)
Pts using ≥3 QTc medications (N=19)	17 (89.5%)	9 (47.4%)

possible risk, but a sizeable number of patients also had exposures the medications categorized as risk and conditional risk. Forty seven (31.3%) patients were exposed to 2 or more QT-prolonging medications, including patients with 3, 4, or 5 concurrent QTc prolonging medication exposures.

When grouped by drug class, the most commonly prescribed QTc-prolonging medications included antiemetics, antidiarrheals, antianginal agents, typical and atypical antipsychotics, antimicrobials, and antiretrovirals. When considering individual agents, the most commonly prescribed agents categorized as risk for TdP included azithromycin and citalopram. The most commonly prescribed medications categorized as conditional risk were ondansetron and quetiapine. For possible risk medications, the most common exposures were to diphenhydramine and trazodone.

The majority of patients (74.7%) had an ECG completed upon admission. However, only 28 of these patients (17.3%) had a follow-up ECG performed during their hospitalization. Approximately half of the patients (50.7%) with ECGs performed had a borderline or abnormal QTc interval during admission. Of the 28 patients with a follow up ECG performed, 10 patients (6.7%) had new onset QTc prolongation during hospitalization. Interestingly, among the five patients who had a follow-up ECG available and no QTc medication exposure, 4 (80%) experienced new onset QTc prolongation. Of the 18 patients with exposure a QTc prolonging medication who had a follow-up ECG, 6 (33.3%) experienced new onset QTc prolongation. We did not find a significant difference in the occurrence of new onset QTc prolongation between patients with and without exposure to a QTc prolonging medication (p=0.127). Furthermore, when considering patients who were concurrently prescribed multiple medications with QTc prolongation risks, we did not find a significant difference in new onset QTc prolongation when compared to patient of one or no exposure (30.8% vs. 60%; p=0.222).

Table 3 shows ECG performance categorized by QTc prolonging medication exposure. An increasing percentage of patients had a follow up ECG performed as their number of QTc prolonging medication exposures increased. When patients had 3 or more QTc prolonging medication exposures, close of half of these patients received a follow-up ECG during their hospitalization.

Discussion

This represents one of the few epidemiological studies to examine the prevalence of QTc medication exposures among hospitalized patients. In addition to numerous other risks for acquired QTc prolongation, hospitalized patients have a substantial exposure risk to medications that may prolong the QTc interval. Additionally, nearly a third of patients in this study were concurrently prescribed multiple QTc-prolonging medications. These types of pharmacodynamic interactions can further increase the risk for QTc prolongation and clinical sequalae.

With these risks in place, the inpatient setting offers a convenient opportunity to provide ECG monitoring relative to the outpatient setting. Although the majority of patients in this study population received ECG testing upon admission, a minority of patients had follow-up ECG testing during their hospitalization. Without follow up testing, it is difficult to discern a temporal relationship between drug exposure and QTc prolongation. While not statistically significant, patients with multiple QTc medication exposures were more likely to receive follow up ECG testing. Regardless, the majority of patients with QTc medication exposure did not receive follow up ECG testing and as a result the presence of medication-induced QTc prolongation may be going undetected. Furthermore, the retrospective design of this study makes it difficult to discern if ECG testing was performed specifically because of medication exposures or for some other reason.

This study attempted to examine the association between QTc prolongation with medication exposure. The lack of follow up ECG testing, however, severely limited our ability to adequately study this end point. Although there were a significant number of patients with abnormal QTc intervals, most were discovered upon admission and not with the follow up ECG. When analyzed, we found that the presence of an abnormal QTc interval was statistically similar between patients with and without QTc prolonging medication exposures, although it was numerically higher among patients without a QTc prolonging medication exposure. It is important to note that this study did not have sufficient power to adequately analyze this end point and a well powered, prospective, randomized control trial is necessary to optimally study this endpoint.

When considering the types of medication exposures, there was a mixture between medications continued from home and newly prescribed medications. Most of the newly prescribed medications were antimicrobials and antiemetics. For patients who were concurrently prescribed multiple QTc prolonging medications, this was often a mixture of a home medication and a new medication prescribed during the hospitalization. For prescribers and pharmacists, the addition of a new QTc prolonging medication to an existing QTc prolonging medication regimen deserves careful consideration. A risk-benefit approach is the generally accepted approach to this clinical dilemma, but the use of ECG testing represents an important tool particularly within the inpatient setting. The majority of patients in the current study did not receive a followup ECG when a new QTc prolonging medication was prescribed. It remains difficult to delineate the proper approach to such situations instead, decisions need to be made on a case by case basis. This study highlights the lack of ECG data available when considering these risks and poses the question of whether ECG testing should be more common for patients with multiple exposures to QTc prolonging medications.

This study has several limitations. Firstly, we did not examine all variables that may cause QTc prolongation in the patient population. Data on factors such as electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), history of a prolonged QTc interval in individual patients, TdP or cardiac arrest, coronary artery disease, left ventricular systolic dysfunction and liver disease were not included in the analysis. As mentioned previously, the retrospective design of this study makes it difficult to ascertain the temporal relationship between QTc prolonging medications exposures and ECGs. In addition, the incidence of new onset QTc prolongation during hospitalization was low. Thus, there was inadequate power to link QTc prolongation episodes during hospitalization to causative

medication exposures. As this is an epidemiological study, the findings cannot be attributed to cause-effect and no direct relationship between variables can be inferred with certainty.

Conclusion

In conclusion, hospitalized patients are commonly prescribed single and multiple QTc prolonging medications. Although we found a substantial number of patients had an abnormal QTc interval upon admission, few patients experienced new onset QTc prolongation. Due to the small sample size and epidemiological design of this study, a significant association between medication exposure and new onset QTc prolongation was not detected. Enhanced ECG monitoring for hospitalized patients with QTc prolonging medication exposures may be prudent, but this study cannot provide definitive data to guide this practice.

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