American Journal of Emergency Medicine 46 (2021) 156–159

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

QT interval prolongation and the rate of malignant ventricular dysrhythmia and cardiac arrest in adult poisoned patients

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ARTICLE INFO

Article history:
Received 9 April 2021
Accepted 25 April 2021
Available online xxxx

Keywords:
QTc interval
Drug induced QTc prolongation
Ventricular dysrhythmia
Malignant ventricular dysrhythmia
Cardiac arrest
Ingestion
Overdose
Poisoning

ABSTRACT

Introduction: Prolongation of QTc interval, a common electrocardiographic (ECG) abnormality encountered in the toxicology patient, is reportedly associated with an increased risk of malignant ventricular dysrhythmias (MVD), such as ventricular tachycardia (VT, with and without a pulse), ventricular fibrillation (VF), and/or cardiac arrest. Quantifiable cardiac arrest risk in relation to specific QTc interval length is not known in this population.
Methods: We conducted a retrospective, observational study to assess the rate of cardiac arrest and its association with degree of QTc prolongation in a cohort of patients requiring toxicology consultation.
Results: 550 patients were included in our analysis (average age 36 years and 49% male). Average QTc was 453 milliseconds (ms). Overall incidence of cardiac arrest in the study cohort was 1.1% with 6 reported cases; when considering patients with QTc > 500 ms, incidence was 1.7%. Two patients with cardiac arrest experienced ventricular dysrhythmia with decompensation prior to cardiac arrest; four patients developed sudden cardiac arrest.
Conclusions: The risk of malignant ventricular dysrhythmia, including cardiac arrest, is low in this poisoned patient population with an overall rate of 1.1%. Two-thirds of cardiac arrest cases occurred in patients with normal QTc intervals. When considering patients with prolonged QTc intervals, the rate of cardiac arrest remains very low at 0.8%. Considering QTc greater than 500 ms, the rate of cardiac arrest is 1.7%. Further prospective studies are required to quantify the risk of malignant ventricular dysrhythmias, including cardiac arrest, and its relation to the degree of QTc interval in poisoned patients.

1. Introduction

The interpretation of the electrocardiogram (ECG) and application of the clinical information obtained from the ECG to patient care is an important part of acute, emergency, and critical care. This ECG information can include ST segment deviation, morphologic anomalies, and interval abnormalities, among many other vital clinical data points. One such data point, the QTc (corrected QT) interval, is a very important portion of the P-QRS-T electrical cycle. This interval, the ECG structure that begins with the QRS complex and terminates at the end of the T wave, represents the time period during which the ventricular myocardium depolarizes and subsequently repolarizes.

The prolonged QTc interval is associated with an increased risk of malignant ventricular dysrhythmias, such as ventricular tachycardia (VT, with and without pulse), ventricular fibrillation (VF), and/or sudden cardiac death (SCD). QTc interval prolongation is associated with a range of clinical scenarios and medical diagnoses, including toxicologic presentations (both excessive ingestion and regular use of medications), electrolyte abnormalities, genetic syndromes, and various acute and chronic ailments (myocardial ischemia, central nervous system hemorrhage, etc) [1]. This association of prolongation of the QTc interval with malignant dysrhythmias with or without sudden cardiac death has been known for many years [2]. In fact, it is widely known in medicine that progressively longer QTc intervals are associated with increasingly higher risk of malignant ventricular dysrhythmia. Despite this known association, estimated risk of adverse dysrhythmia outcome in relation to specific QTc interval length is not known.

The medical literature addressing this topic in the toxicologic patient population includes numerous observational studies investigating the effect of various medications known to prolong the QT interval [3-5] and outcomes in patients with drug induced prolonged QT interval [6-8]. There is minimal data on the rate of dysrhythmic events in the general toxicologic population and how this rate is affected by progressive

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https://doi.org/10.1016/j.ajem.2021.04.077
0735-6757/

prolongation of the QTc interval. The aim of the present study was thus to determine the rate of malignant ventricular dysrhythmia and/or cardiac arrest in a cohort of patients requiring toxicology consultation and to assess how rates of cardiac arrest change with progressive lengthening of the QTc interval.

2. Methods

We conducted a retrospective chart review of a pre-established Toxicology-ECG database, comprised from a cohort of patients receiving consultation by the Medical Toxicology service at a tertiary care academic center. This study was approved by the Internal Review Board at the University of Virginia School of Medicine.

All records in the database from January 2016 to January 2018 were searched. Cases were included if a QTc interval measured on first in-hospital (i.e., not emergency medical services [EMS]) ECG and outcome data for the encounter were available. The primary outcomes were occurrence of malignant ventricular dysrhythmia (ventricular tachycardia [with and without a pulse], ventricular fibrillation, and/or cardiac arrest. Patients with a corrected QT interval < 350 ms were excluded in order to enable comparison of arrest rates in patients with a prolonged QTc interval to those in patients with a normal QTc; we did not want cases of arrest related to a shortened QTc interval to confound our findings. The first available in-hospital ECG was used for QT interval measurements and other ECG data. Corrected QT intervals were calculated using Bazett formula and QT intervals measured electronically.

2.1. Toxicology – ECG database

Medical documentation from the Blueridge Poison Center was used to identify patients requiring a toxicology consultation at the University of Virginia. All identified patient encounters were reviewed by one of three trained investigators (LR, CB, MS). Poison center records and the University of Virginia electronic medical record were used to extract patient demographics, exposure agent and reason for exposure, ECG findings, treatment modalities, and outcomes. This information was then input into a Microsoft Access® V15 (Microsoft, Redmond, WA) file. The database included information related only to the encounter for which a toxicology consult was placed.

2.2. Data analysis

Identified cases were grouped based on QTc intervals lengths. Patients reported to have experienced cardiac arrest during their encounter were identified and rates of arrest were calculated within each QTc group. Further statistical analysis was not performed given the low incidence of arrest in our study cohort.

3. Results

There were 566 entries recorded in the Toxicology-ECG database, 550 were included for analysis in this study. Refer to Fig. 1 for a depiction of all patients in this study. Thirteen were excluded because of missing outcome data and three were excluded because they were found to have a short QTc interval (<350 ms). Table 1 lists demographic, ECG, and medication/chemical exposure data for patients included in the study cohort. Average age was 36.2 years with 48.8% male gender. The most common reason for presentation was suspected suicide attempt (42.7% of patients). Other reasons for toxicology consultation included drug abuse/misuse (23.5%) and unintentional exposure (10.4%). The most common exposure agent was alcohol, followed by an unknown agent, an opioid, and a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Average QTc interval of the entire study cohort was 453.1 +/− 36.7 ms. The average QTc interval of patients who ultimately experienced arrest was 459.2 +/− 68.0 ms. The vast majority of included patients (97.9%) survived to hospital discharge.

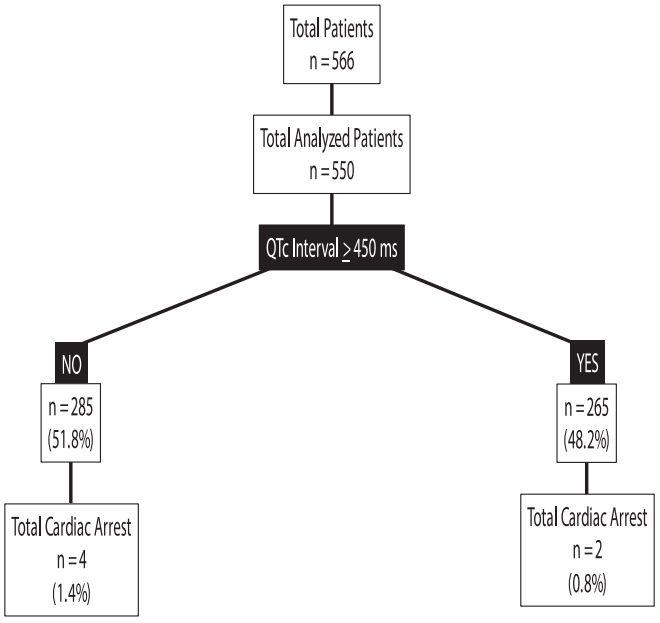

Fig. 1. Depiction of study patients with respect to abnormal QTc interval (defined as ≥450 ms) and occurrence of cardiac arrest.

Approximately half of patients in the study cohort (285 of 550 patients) had a QTc interval that was within normal limits (Fig. 1). The incidence of cardiac arrest was low in our study population with only six patients reported to have experienced arrest (overall incidence 1.1%). Within this group of six cardiac arrest patients, two patients had a preceding episode of ventricular dysrhythmia which decompensated further to cardiac arrest. Among patients with QTc ≥500 ms, incidence of cardiac arrest was low (1.7%). When rates of cardiac arrest were compared across QTc ranges, the rate was highest in the group with QTc

Table 1
Demographic, ECG, and exposure data on toxicology consult patients included in the study cohort.

Total Patient Events	$n = 550$
Demographics	
Age (SD)	36.2 (17.7)
Male (%, n)	48.8 (276)
Fatal outcome (%, n)	2.1 (12)
ECG Data	
Average QTc Interval Length (ms, SD)	453.1 (36.7)
Average QRS Complex Width (ms, SD)	96.7 (58.2)
Exposure Medication/Agent	
Ethanol (%, n)	19.8 (109)
Unknown Drug (%, n)	13.8 (76)
Opioid (% n)	13.3 (73)
SSRI/SNRI (%, n)	11.5 (63)
Benzodiazepine (%, n)	8.0 (44)
Acetaminophen (%, n)	8.0 (44)
Reason for Exposure	
Suspected suicide (%, n)	42.7 (235)
Abuse/Misuse (%, n)	23.5 (129)
Unknown (%, n)	14.4 (79)
Unintentional (%, n)	10.4 (57)
Medication Adverse Event (%, n)	8.2 (45)
Medication Withdrawal Syndrome (%, n)	0.5 (3)
Malicious Exposure(%, n)	0.4 (2)

Table 2
Patients were divided in groups based on QTc interval length. Rates of cardiac arrest within each group were calculated. Patients with QTc 550–600 ms were found to have the highest rate of arrest but only 11 patients were included in this QTc range.

QTc interval range (ms)	Cardiac arrest events (n)	Patient number	Rate of cardiac arrest (%)
350–399	1	14	7.14
400–449	3	271	1.11
450–499	1	206	0.49
500–549	0	45	0.0
550–599	1	11	9.09
600–649	0	2	0.0
650–699	0	1	0.0

interval 550–600 ms, although sample size was low with only eleven patients in this QTc range (Table 2 and Fig. 2).

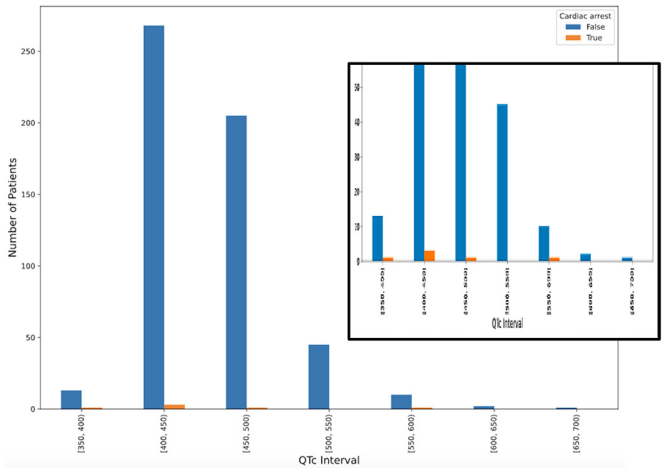

Fig. 2. Patients experiencing (orange bars) and not experiencing (blue bars) cardiac arrest across increasing QTc intervals. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

The present study sought to understand the incidence of cardiac arrest and its relationship to degree of QTc interval prolongation in a cohort of patients requiring toxicology consultation. The cohort consisted of a relatively young patient population (average age 36.2 ± 17.7 years) and many (43%) were presenting for medical care following a suspected suicide attempt. Approximately half of our cohort was found to have a corrected QT interval within normal limits upon initial presentation to the hospital. Additionally, the overall incidence of cardiac arrest was low in our cohort; only 6 of 550 patients (1.1%) ultimately experienced arrest. Even among patients with QTc > 500 ms on initial ECG, only 1 of 59 patients (1.7%) ultimately experienced cardiac arrest. In the six cardiac arrest cases, medications and toxins were identified in five individuals, including: diphenhydramine, bupropion, SSRI, SNRI, tricyclic antidepressant agent, opiate (2 patients), cyclobenzaprine, ethanol (2 patients), and cocaine; in one case, medications and/or toxins were not able to be identified. In those patients with cardiac arrest, there was no common theme regarding medication nor toxin exposure.

Data on QTc prolongation and its association with malignant dysrhythmia events in the poisoned patient are rare. Manini et al. conducted a case control study in suspected poisoning patients; they selected 34 patients with suspected poisoning complicated by an adverse cardiovascular event and 101 suspected poisoning patients who did not experience such an event. Fifteen case patients experienced cardiac arrest. When comparing subjects with a normal, prolonged, or significantly prolonged (>500 ms) QTc intervals, rates of cardiac arrest were similar in patients in the normal and prolonged QTc groups but significantly higher in the group with QTc >500 ms, suggesting increased risk of arrest for the suspected poisoned patient with a corrected QT interval in this range [9].

Vandael et al. studied psychiatric inpatients receiving treatment with more than one QTc prolongating medication. One hundred fifty-two patients were followed for two weeks after initiation of a second drug known to cause QTc prolongation; three patients developed a prolonged QTc interval but there were no cases of sudden cardiac death or torsade de pointes [3]. This low rate of arrest in patients treated with QTc prolonging drugs is in agreement with the low rate of arrest reported in the present study.

Additional data is derived from studies on patients with drug induced QTc interval prolongation. Many of these studies report higher rates of arrest than were reported among patient with prolonged QTc interval in the present study. De Vecchis et al. studied 73 patients with drug induced QTc interval. Median QTc was 501 ms and 74% had QTc interval > 500 ms. They report that 63% of their cohort experienced arrest, dysrhythmia, or syncope [6]. Similarly, Letsas et al. studied 21 hospitalized patients with drug induced QTc prolongation. Average QTc interval in their cohort was 542 ms. Six of twenty-one (28.5%) patients experienced torsade de pointes and they report a correlation between a QTc interal >510 ms and arrest or TdP [8].

The current study is limited by the number of cases of cardiac arrest that were identified in the study cohort. Only six cases of arrest were identified and thus our data does not enable sufficient comparison of arrest rates across varying degrees of QTc prolongation. Furthermore, these patients were a select group who received a consultation from the Medical Toxicology service and therefore may not be representative of a larger population of overdose patients. It is not known if patients received antidotes such as magnesium and what effect this may have had on cardiac arrest. In addition, it is not known in every case that dysrhythmia was the cause of cardiac arrest; in other words, the patient could have experienced a compromised airway causing hypoxia, hypercarbia, and acidosis with resultant cardiac arrest. Lastly, because this study was conducted via chart review, its results are dependent on the quality and quantity of documentation performed.

5. Conclusion

The risk of malignant ventricular dysrhythmia, including cardiac arrest, is low in this poisoned patient population with an overall rate of 1.1%. Two-thirds of cardiac arrest cases occurred in patients with normal QTc intervals (i.e., less than 450 ms). When considering patients with prolonged QTc intervals (i.e., greater than or equal to 450 ms), the rate of cardiac arrest remains very low at 0.8%. Considering QTc greater than 500 ms, the rate of cardiac arrest is 1.7%. Further prospective studies are required to more accurately quantify cardiac arrest risk and its relation to the degree of QTc interval prolongation in this population of poisoned patients..

Declaration of competing interest

None.

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