Recommendations for QTc Monitoring:
Rational or Arbitrary?

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LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Have you ever wondered if and how often an electrocardiogram (EKG) should be obtained to monitor the QTc? Have you been unclear about which medical and metabolic conditions and medications can prolong the QTc? If you have, then this case of an elderly man with symptoms referable to multiple organ systems and treatment that involved several agents with QTc-prolonging side effects should prove helpful. We use this case as a stimulus for discussion, review the risk-benefit analysis for medication administration and monitoring, and discuss the rationale for daily QTc monitoring.

CASE VIGNETTE

Mr A, a 68-year-old man with a history of smoking, chronic obstructive pulmonary disease (COPD), heart failure (with a preserved ejection fraction), chronic lower back pain, posttraumatic stress disorder (PTSD), depression, and insomnia, was admitted to the hospital with fever, acute-onset dyspnea, cough, and lower-extremity edema. He had been in his usual state of health until 3 days earlier when he developed bilateral lower-extremity edema. The following day, he felt feverish and increasingly dyspneic and was coughing. His dyspnea worsened over the next 2 days, and he came to the emergency department (ED) for evaluation.

On arrival to the ED, he was noted to be afebrile; however, his heart rate was 152 bpm, he was tachypneic, and his blood pressure was 85/56 mm Hg. The physical examination was notable for respiratory distress, diffuse wheezing, and mild symmetric bilateral lower-extremity edema. Mr A was treated with 2 L of crystalloid fluid, and he was started on bilevel positive airway pressure. Laboratory evaluation revealed a neutrophil-predominant leukocytosis to 18.9 cells/mm^3, and his chest x-ray showed a patchy opacity in the left lung base. His initial EKG revealed sinus tachycardia with a QTc of 441 ms. Mr A received ipratropium-albuterol nebulizers, intravenous (IV) methylprednisolone, and IV magnesium, as well as vancomycin and cefepime for a presumed COPD exacerbation that was triggered by pneumonia. His antibiotic regimen was quickly modified to levofloxacin (750 mg daily) for treatment of community-acquired pneumonia.

Mr A took methadone (20 mg 4 times daily), tizanidine (8 mg twice daily), and pregabalin (200 mg 3 times daily) for chronic low back pain; mirtazapine (45 mg nightly) and quetiapine (250 mg daily) for persistent depression; and trazodone (200 mg nightly), prazosin (2 mg), and zolpidem

Clinical Points

- Patients are often treated with multiple medications, and many of these agents can prolong the QTc interval (directly or indirectly via drug-drug interactions) and contribute to life-threatening arrhythmias.
- Providers should exercise caution when considering the addition of a QTc-prolonging medication for a patient with multiple preexisting risk factors or QTc-prolonging medications, even in a monitored setting.
- Although we have cost-effective means of evaluating the QTc, as well as consensus guidelines for monitoring, definitive data derived from implementation of these recommendations are lacking.

(5 mg intermittently) for severe insomnia secondary to posttraumatic stress disorder (PTSD).

Given his borderline elevated QTc (441 ms), use of multiple medications known to affect the QTc, and the recent addition of levofloxacin (750 mg daily) to his medication regimen, the medical team obtained a daily EKG to monitor for the development of QTc prolongation.

DISCUSSION

Across the United States, patients who require hospital-level care are typically treated with multiple medications, and many of these agents prolong the QTc interval, directly or indirectly, via drug-drug interactions (Table 1). Unfortunately, when the QTc increases to > 440 ms, the risk of R on T phenomena and lethal arrhythmias (eg, torsades de pointes [TdP], ventricular tachycardia, ventricular fibrillation) also increases. Clinicians' fears of inducing QTc prolongation and lethal arrhythmias lead to frequent monitoring (eg, via daily EKGs or an EKG after each dose increase of a medication associated with QTc prolongation). These monitoring strategies are accompanied by costs (eg, of time, effort, and money) and are often associated with undue concern by patients, providers, and systems of care (eg, concern over liability if diligent monitoring does not occur).

What Is the QTc and What Prolongs It?

The QT interval is the time between the start of ventricular depolarization and the end of ventricular repolarization. On a standard 12-lead EKG, the QT interval is measured from the junction of the isoelectric baseline and first negative deflection in the QRS complex to the end of the T wave, specifically, to the point where the tangent with maximum slope (second half of the T wave) intersects with the isoelectric line. The QT interval is rate-dependent, and reference values are normalized to heart rate, generating the QTc or the QT interval divided by the square root of the R-R interval. Measurements of QTc are imperfect and depend on the lead being analyzed, with leads II, V5, and V6 yielding the most accurate measurements. Furthermore, the QTc varies from moment to moment and is dependent on several factors including, but not limited to, autonomic tone, position, and volume status. The QT interval can also be affected by pharmacotherapies[1]; it is classically prolonged by class I and III antiarrhythmics. Numerous commonly used classes of medications (eg, antipsychotics, antidepressants, analgesics, antibiotics) have also been implicated in QT prolongation.[2,3]

Table1. Drugs That Commonly Prolong the QTc Interval

Antiarrhythmics	Class Ia: disopyramide, procainamide, quinidine
	Class III: amiodarone, sotalol
Antihistamines	Diphenhydramine
Antipsychotics	Conventional agents: chlorpromazine, droperidol, haloperidol, pimozide, thioridazine
	Atypical agents: clozapine, olanzapine, quetiapine, risperidone, ziprasidone
Antidepressants	Tricyclics: amitriptyline, desipramine, doxepin, imipramine, nortriptyline
	Selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine
	Others: bupropion, venlafaxine
Antiemetics	Ondansetron
Antibiotics	Macrolides: clarithromycin, erythromycin
	Quinolones: levofloxacin, moxifloxacin
Antimalarials	Chloroquine, quinine
Antiprotozoals	Pentamidine
Antifungals	Fluconazole, ketoconazole
Analgesics	Methadone

Medication-mediated QT prolongation is of clinical importance because it is associated with the development of TdP, a life-threatening polymorphic ventricular tachycardia. Importantly, however, while QT prolongation can precipitate TdP, it is not sufficient by itself. The substrate for this arrhythmia instead relies on the transmural dispersion of repolarization, meaning that the time for ventricular repolarization varies from endocardium to epicardium, allowing for reentrant excitation. This dynamic is best exemplified by the class III antiarrhythmic amiodarone, which prolongs the QTc on the surface EKG but still ultimately suppresses arrhythmias by standardizing repolarization times across the cardiac wall and, thereby, decreasing the risk of reentrance and the generation of TdP.[2]

What Is the Prevalence of QTc Prolongation?

Much of the data on the prevalence of QTc prolongation among inpatients comes from small, single-center studies[4–6] with significant limitations. For those admitted to medical services, some degree of QTc prolongation appears to be common. One prospective study[4] found that 24% of critically ill intensive care unit patients had a QTc > 500 ms. A small retrospective study[5] of elderly patients admitted to an acute geriatrics service noted that 27% had QTc prolongation (defined as ≥ 470 ms in women and ≥ 450 ms in men). Similar rates of QTc prolongation were seen in a prospective observational study of 279 patients in the ED; 34.1% of them had a prolonged QTc interval (defined as ≥ 460 ms in women and ≥ 450 ms in men).[6] The prevalence may be even higher in those with an underlying cardiac disease, as demonstrated by a prospective observational study[7] of cardiac patients that showed that 44.6% had some degree of QT prolongation and 17.3% had a QTc > 500 ms. Interestingly, in a large

retrospective study[8] of 41,649 hospital admissions, only 293 patients (0.7%) had a QTc > 500 ms; this finding most likely reflects that this study was not limited to medical patients (who are more likely to have underlying comorbidities or coadministered medications that contribute to a prolonged QTc).

How Frequently Are QTc-Prolonging Medications Coadministered?

Medical inpatients over the age of 75 years receive a mean of 7.5 drugs each day; thus, the risk of QTc prolongation is increased in this group, as this population is at high risk for delirium and treatment with antipsychotics that prolong the QTc interval.[9] Among inpatients, prescription of antiarrhythmics, antiemetics, antibiotics, analgesics (eg, methadone), or antipsychotics—especially when hypomagnesemic, hypokalemic, and bradycardic—create a "perfect storm." One cross-sectional study[10] showed that 0.9% of psychiatric inpatients had drug-induced QT prolongation and 0.17% sustained TdP or sudden cardiac death. However, more than 85% of those with drug-induced QT prolongation had at least 2 risk factors for QT prolongation (eg, older age, female sex, electrolyte abnormalities, renal or hepatic dysfunction, preexisting heart disease, bradycardia, and a genetic predisposition).[10] Unfortunately, medical inpatients possess many of these risk factors. In a retrospective cohort study[11] of 175 medically ill inpatients who received IV haloperidol, 86% had at least 1 risk factor for QT prolongation and 55% had 2 or more risk factors. Pasquier and colleagues[12] found that 22.3% of medical inpatients had a prolonged QTc interval within 24 hours of admission and 50.8% of patients with QTc prolongation received additional QT-prolonging drugs during their hospitalization.

Who Is Most at Risk for Developing QTc Prolongation?

Aside from genetically inherited QTc prolongation syndromes, risk factors for QTc prolongation include female sex, older age,[13] structural heart disease, renal or hepatic dysfunction, hypothyroidism, and bradycardia. Additional potentially modifiable risk factors include electrolyte depletion and rapidly administered medications. Patients at greatest risk tend to possess several risk factors. In general, women have slower ventricular repolarization times and thus have longer QTc intervals. Interestingly, this change is only seen after puberty, leading some to consider the effect of sex hormones on drug channels.[14,15] One study[16] even suggested a variation in QTc depending on the phase of the menstrual cycle. Renal or hepatic dysfunction may lead to decreased drug clearance and to accumulation of QTc-prolonging metabolites. Elderly individuals may have higher sympathetic activity or changes in cardiac tissue (eg, secondary to amyloid deposits, fibrosis), which may alter repolarization. Hypokalemia and hypomagnesemia can also increase risk of QTc prolongation due to effects on electrolyte channels. Hypomagnesemia is often seen in chronic alcohol use, and inpatients with alcohol use disorder are at a higher risk of QTc prolongation.

A review of case reports[17] of drug-induced TdP associated with noncardiac drugs identified (1) female sex, (2) organic heart disease, (3) hypokalemia, (4) familial history of a long QT syndrome, (5) drug toxicity secondary to kidney or liver failure, (6) excessive doses of medications or drug interactions, and (7) simultaneous use of more than 1 QT-prolonging drug as easily identifiable risk factors for development of TdP.

When Should We Worry About QTc Prolongation?

The clinical concern related to QTc prolongation is often attributed to the resultant risk of arrhythmias such as TdP. TdP (a French term that translates to "twisting of the points") is a fast, unstable, and polymorphic ventricular arrhythmia that either self-terminates or deteriorates into ventricular fibrillation. A large prospective trial[18] demonstrated that QTc prolongation is an independent predictor of mortality, even in a healthy population with no known cardiovascular risk factors. In a 28-year follow-up period, QTc prolongation was linked not only to an increased risk of all-cause mortality, but also to increased mortality due to cardiovascular and ischemic heart disease.[18] Researchers have sought to quantify the relative risk of cardiac arrhythmias on the basis of the degree of QTc prolongation. One suggested hazard ratio for cardiac events linked to prolongation of the QTc is 1.052^{x} wherein x is an increase of 0.01 $sec^{1/2}$ ms in the QTc.[19] For example, a patient with a QTc of 0.60 $sec^{1/2}$ would have a 2.76-fold greater risk of experiencing a subsequent cardiac event per unit of time than a subject with a QTc of 0.40 $sec^{1/2}$. In addition, several patient characteristics have been identified as risk factors for the development of TdP. In 1 study,[17] 96% of cases of TdP had at least 1 risk factor for TdP, and 72% of cases had at least 2 risk factors. However, the per-person risk of a hazardous cardiac event was relatively low.[17] One recent systematic review[20] looked at 14,756 patients exposed to QTc-prolonging medications. Of the 930 patients (6.3%) with QTc prolongation, 379 patients (2.6%) developed ventricular arrhythmias and TdP was found in 49 patients (0.33%), while sudden cardiac death was established in 5 patients.[20]

What Recommendations Exist for QTc Measurement and Monitoring?

The most recent and comprehensive guidelines for tracking the QTc were published by the American Heart Association (AHA) in 2017.[21] These guidelines were based on the class of the recommendation and the strength of evidence supporting those claims. Even for class I recommendations (eg, benefits greatly outweigh risks, procedure/treatment should be performed/administered), the authors[21] put forward general principles for QTc monitoring rather than specific practice recommendations. For example, patients with a class I indication for QT monitoring should have documentation of the QTc (including a rhythm strip) in the patient's medical record at baseline and then at least every 8 to 12 hours. Only some aspects of how to measure or to monitor the QTc were defined. The authors[21] established standards for measuring the QTc and defining what was meant by a prolonged QTc

but admitted that the ideal method for correction of the QTc for heart rate was less clear and was informed by only some data favoring Hodges, Framingham, and Fredericia formulae relative to the Bazette formula. No specific recommendation was made regarding the method of QTc monitoring (eg, manual, semiautomated, or fully automated continuous monitoring) due to a lack of evidence supporting a "gold standard" as well as a wide range of monitoring capabilities of hospitals across the nation. Instead, they insisted on consistency in the use of a methodology within institutions.[21]

The AHA recommendations for QTc monitoring[21] are stratified and based on a patient's risk factors for TdP (eg, their medications). Patient risk factors for TdP in the AHA guidelines include older age (cutoff unspecified), female sex, and a preexisting heart condition (including myocardial ischemia and a low left ventricular ejection fraction, bradyarrhythmia, an electrolyte abnormality, renal or hepatic failure, and concomitant use of drugs that prolong the QT interval). Class I indications for QTc monitoring exist for patients newly started on an antiarrhythmic (with a known or possible risk of TdP regardless of patient TdP risk factors), patients with risk factors for TdP who are started on nonantiarrhythmic drugs with a known risk of inducing TdP, and patients with severe electrolyte abnormalities (regardless of the patient's medication regimen). Class III indications (QTc monitoring is not recommended; no benefit) exist for patients with no risk factors for TdP who are started on nonantiarrhythmic drugs that have been associated with a risk for TdP.

The majority of the AHA guidelines,[21] even those carrying class I recommendations, are supported by level C evidence (very limited populations evaluated, only consensus opinion of experts, case studies, or standard of care). Whereas some of these designations were derived from widely accepted standards of care that have not been rigorously studied and likely do not demand further investigation, other less commonly followed practices highlight gaps in the literature that would benefit from additional study. Of particular interest is the effect of QTc monitoring on detection of TdP and mortality associated with QTc prolongation.

While others[22,23] have proposed recommendations for QTc monitoring mostly involving various psychiatric medications, we were unable to find other consensus guidelines that have been supported by major national societies. Recommendations for QTc monitoring during drug development have been published by the US Food and Drug Administration (FDA)[24] that target the pharmaceutical industry. These guidelines have established specific practices for QTc monitoring (eg, use of Fredericia's formula to determine the rate-corrected QTc) in the evaluation of novel agents; however, these recommendations do not directly translate into practical guidelines for clinicians after the medications have been approved. Although the aforementioned recommendations are not legally enforceable, the FDA maintains the authority to issue warnings and to deny approval for new and preexisting agents.[23]

Is It Cost-Effective to Monitor the QTc?

The costs associated with monitoring QTc segment length with a resting EKG need to be considered. A standard 12-lead EKG is widely considered a low-cost test with no major risk. While the Medicare reimbursement and fee schedule estimated that a routine EKG (with interpretation) costs between $10 and $20,[25] a study[26] that subsumed all relevant costs (eg, EKG, facility, physician management) associated with the management of QT monitoring estimated the total cost to be approximately $200 and concluded that systematic EKG screening helps reduce the number of sudden cardiac deaths in a cost-effective manner. Hospital admission, specifically for initiation of antiarrhythmic therapy, with active monitoring of the QTc has also been found to be cost-effective.[27] Nonetheless, downside financial risks and medical-legal liability should be taken into account when considering the total costs associated with QTc monitoring.[28,29]

CASE DISCUSSION

The case of Mr A helps to frame the dilemmas associated with monitoring the QTc. Given his multiple risk factors (elderly status, heart failure, hypoxemia, and hypotension), initial borderline prolonged QTc (441 ms), the addition of an antibiotic (levofloxacin) that can increase the QTc interval, and an analgesic (methadone) known to prolong the QTc, it is understandable why daily EKGs were ordered and monitored. Until further studies codify specific monitoring routines, we would support the use of daily EKGs for patients fitting Class I recommendations while new medications are being added or dose adjusted with a low threshold to stop daily monitoring once stability in the dose and the interval is obtained. While the cost-effectiveness of EKGs has been detailed previously, the utility of telemetry monitoring of the QTc in otherwise stable patients is less supported by the literature. Finally, given the overall prevalence of QTc prolongation alongside its association with mortality, we would advocate that providers exercise caution when considering the addition of a QTc-prolonging medication in a patient with multiple preexisting risk factors or QTc-prolonging medications—even in a monitored setting.

CONCLUSION

Prolongation of the QTc is a common phenomenon associated with life-threatening arrhythmias. There are clearly defined risk factors for QTc prolongation related to medications as well as patient substrate. We have cost-effective means of evaluating the QTc as well as consensus guidelines for monitoring the QTc, but comprehensive data informing these recommendations is lacking and the gold standards of frequency and modality of monitoring have yet to be elucidated. Future directions entail defining more specific monitoring intervals and interrogating the effect of QTc monitoring on lowering the mortality associated with QTc prolongation.

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