CLINICAL PRACTICE

Clinical Vignettes

Quinine and the ABCs of Long QT: A Patient's Misfortune with Arthritis, (Alcoholic) Beverages, and Cramps

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A 91-year-old woman presented to the emergency department by ambulance after her family found her minimally responsive. Telemetry monitoring demonstrated episodes of non-sustained polymorphic ventricular tachycardia (PMVT) associated with significantly prolonged repolarization. Her medical history revealed that she was taking quinine or a derivative in three different forms: hydroxychloroquine, quinine sulfate (for leg cramps), and her gin mixed with tonic water (containing quinine). The present case is illustrative of classic etiologies and findings of acquired long QT syndrome, and serves as an important reminder for providers to take a complete medication history, including use of duplicative and alternative medicines and type of alcohol consumption.

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CASE

A 91-year-old woman presented to the emergency department (ED) by ambulance after her family found her minimally responsive amidst her own stool and emesis. Upon arrival at the hospital, the patient was confused and combative. Given her agitation, she was sedated shortly after arrival to the ED, which left her unable to give a clear history. The rest of her history was gathered from her family, which revealed 2 weeks of cough and decreased appetite, and the day prior to presentation she had nausea, vomiting, and diarrhea.

According to the family, the patient was in her usual state of health prior to presentation. She had a history of rheumatoid arthritis, for which she took hydroxychloroquine (HCQ, Plaquenil). Additional history was notable for taking quinine sulfate for leg cramps (prescribed by her family practice provider) and consumption of a “nightcap” alcoholic beverage of gin and tonic each night.

On initial examination, the patient was drowsy and sedated but arousable. She responded to questioning but exhibited garbled speech that was difficult to interpret. Her mental status waxed and waned; she was not oriented to place or situation. Her initial cardiac exam revealed a heart rate of approximately 50 beats per min (bpm) and frequent ventricular ectopy on

telemetry. Her lab results were notable for lactate of 3.3 mmol/L and troponin I of 0.22 ng/mL. Serum potassium was 3.4 mEq/L and serum magnesium was 1.8 mEq/L.

After initial examination, telemetry monitoring in the ED demonstrated episodes of repetitive, non-sustained polymorphic ventricular tachycardia (PMVT). The patient was started on amiodarone and transferred to the medical ICU. Throughout her first hospital night, the bradycardia became more marked, thought to be due to an effect of the amiodarone. An ECG demonstrated significant sinus bradycardia with frequent ectopic beats, and a measured QT interval >800 msec (Fig. 1). She also continued to have non-sustained PMVT on telemetry, which appeared torsadogenic due to the pause-dependent prolongation of the QT interval leading into PMVT. An ECG showed a ventricular ectopic beat (a presumed ventricular extrasystole) in an “R-on-T” pattern that initiated PMVT in a more prolonged “torsades de pointes” pattern, which was not sustained (Fig. 2). An echocardiogram demonstrated moderate left ventricular hypertrophy with a preserved ejection fraction.

Once her immensely prolonged QT interval was noted, amiodarone was discontinued and lidocaine started as a potential “QT shortener,” as well as isoproterenol to lessen the impact of her bradycardia on QT prolongation. She continued to improve over the next few days, and her QT interval ultimately normalized.

Finally, the last contributing factor to her quinine toxicity was her acute illness, which was thought to be viral given the lack of leukocytosis or other signs of sepsis. Her viral illness with associated anorexia and volume depletion likely exacerbated the effects of her quinine toxicity, which manifests classically as nausea, vomiting, and diarrhea. The initial bradycardia may have been vagally mediated in the setting of nausea and vomiting. With volume resuscitation and cessation of her quinine-containing medications, these symptoms resolved. As her mental status cleared, the first clear speech she gave was “May I please have my leg cramp pills?” This request was politely declined.

DISCUSSION

Acquired long QT syndrome (ALQTS) is an electrophysiological cardiac condition most commonly induced by drugs. Generally, drugs that cause QT prolongation do so by blocking

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Figure 1 Electrocardiogram upon arrival at emergency department. Note the bradycardia, as well as the significantly prolonged QT interval (measured at >800 msec). There are also ventricular extrasystoles (arrows), which nearly fall on the T waves of the preceding repolarization.

the delayed rectifier current I_{Kr} , the early and rapid current of potassium excursion from cardiac cells during phase 3 of the cardiac myocyte action potential.^{1,2} Drugs or channelopathies that prolong repolarization typically lengthen phase 2 or phase 3, reducing the repolarization current.³ This prolongation of action potential duration exacerbates the (normal) electrical heterogeneity within the myocardium.³ During the lengthened repolarization, some myocytes may give rise to “early afterdepolarizations” (EADs), that is, depolarizing the myocyte prior to completed repolarization. An EAD is manifested on the surface ECG as an R wave superimposed on a T wave (“R-on-T”). Because of the differential among the myocardium regarding cells in varying states of repolarization, this EAD can set up a reentrant circuit within the myocardium owing to voltage oscillation.^{3,4} On the surface ECG, then, one sees an “R-on-T” followed by an oscillatory wave of PMVT, known as torsades de pointes, owing to its undulating

appearance of twisting points. Such arrhythmias can cause syncope, seizures, and sudden cardiac death.^{1,2} Most patients who develop torsades de pointes have predisposing risk factors such as prolonged QT (acquired or congenital), electrolyte abnormalities, or female gender. The QT interval is dynamic, varying with each beat, and is also affected by age, autonomic tone, myocardial ischemia, and structural heart disease.^{2,5}

During our patient’s initial hospital course, it was revealed that she was taking quinine or a derivative in three different forms: hydroxychloroquine (HCQ), quinine sulfate (for leg cramps), and her gin mixed with quinine-containing tonic water. Other causes of ALQTS, such as cardiac ischemia and electrolyte abnormalities, were explored and excluded. Electrocardiographic abnormalities have been reported with excessive use of both quinine and HCQ independently. Both drugs block inward sodium channels, thereby delaying depolarization and prolonging the QRS complex. They also block

Figure 2 Electrocardiogram showing ventricular extrasystoles initiating frequent runs of non-sustained polymorphic ventricular tachycardia, which spontaneously terminate.

several different potassium channels, lengthening the QT interval.⁵ Some patients may also have subclinical potassium channelopathies that can exacerbate the effect of QT-prolonging drugs even at low doses.⁶ In this case, the patient was taking unknown quantities of these drugs, creating a precarious situation putting her at risk for fatal arrhythmias.^{7,8}

The historical roots of quinine date back at least as far as the 1500s. Quinine is an alkaloid derived from the bark of the cinchona tree, native to the lush forests of South America. The indigenous populations likely discovered the medicinal properties of this “magical” bark and used it to quash the fevers and chills that accompanied many tropical diseases. In the mid-seventeenth century, Jesuit missionaries discovered the secrets of the “Peruvian” or “Jesuit bark” and brought the bark to Spain. Eventually, quinine and other antipyretic alkaloids were isolated from the bark and would become the most effective treatments for malaria until the 1920s (when synthetic antimalarial agents like chloroquine were introduced). Interestingly, the first rendition of the gin and tonic cocktail was discovered in an attempt to create a more palatable antimalarial concoction. During the colonization of India, British soldiers sought ways to tone down the bitter taste of quinine by adding gin, water, and sugar to the mix.⁹ The gin and tonic is still known as the quintessential British drink; as Winston Churchill once stated, “The gin and tonic has saved more Englishmen’s lives, and minds, than all the doctors in the Empire”.¹⁰

Although written accounts of quinine toxicity (“cinchonism”) date back centuries, the cardiac effects of quinine were not widely described until the mid-twentieth century. Tinsley Harrison, the founding editor of *Harrison’s Principles of Internal Medicine*, recounts a story of quinine toxicity in his book, *Principles and Problems of Ischemic Heart Disease*.¹¹ Harrison’s colleague and coauthor, Joseph Reeves, was asked to evaluate former Alabama governor James “Big Jim” Folsom regarding his persistent tinnitus. Mr. Folsom was found to have a prolonged QT on his ECG, a finding thought to be incidental. Keeping with Harrison’s maxim, “The answer is often in the history alone,”¹² Reeves discovered that Folsom consumed multiple gin and tonics each day, and eventually diagnosed quinine toxicity or “cinchonism.” Reeves reportedly advised Folsom to switch to bourbon, and his symptoms disappeared.

In 1994, reports on adverse side effects of quinine prompted the first wave of bans by the Food and Drug Administration (FDA) on over-the-counter availability of quinine and marketing of quinine-containing prescriptions.⁷ At that time, quinine was used in the USA primarily as a prophylaxis for people traveling to malaria-endemic regions, but it was also used to treat nocturnal leg cramps. Its efficacy and safety profiles, particularly regarding its use for treating leg cramps, were and have remained controversial.^{13,14}

Doctors have been prescribing quinine for nocturnal muscle cramps since the 1940s, a practice that has continued despite numerous FDA warnings regarding the risks and questionable efficacy. The precise mechanism by which quinine may help muscle cramps is unknown, but one hypothesis is that it decreases the excitability of the motor end plate, reducing muscle contractility.¹⁵ A Cochrane review¹⁶ analyzed 23 trials in which quinine was compared to a placebo (20 trials), vitamin E (four trials), a quinine–vitamin E combination (three trials), a quinine–theophylline combination (one trial), and Xylocaine injections (one trial). The reviewers concluded that there was low-quality evidence that quinine significantly reduces the number of cramp days and moderate-quality evidence that quinine reduces the intensity of cramps.

The FDA has banned the use of prescription quinine-containing medications for any indication other than malaria. Nevertheless, there is literature to suggest that these drugs are often used off-label for nocturnal leg cramps. Furthermore, quinine is still widely available in grocery stores in the form of tonic water, as the FDA eventually allowed for carbonated beverages to contain small concentrations of quinine. Today, tonic water generally contains much less quinine, since it is no longer used as an antimalarial. A standard glass contains roughly 20 mg of quinine, which is much less than a typical 200–300-mg dose for the treatment of leg cramps. Nonetheless, such beverages are not mandated to list the concentrations or the health risks of quinine on the label.^{13,14}

Despite its questionable efficacy and safety, many still use quinine to alleviate nocturnal muscle cramps. The relief many patients feel from quinine—albeit perhaps largely a placebo effect—is difficult for providers to dismiss. In general, it appears that 200–300 mg of quinine a night is probably safe in a person who is closely monitored and who has no contraindications. Therefore, patients will likely continue to request

Table 1 Mechanisms of Prolonged QT in Common Drug Classes

Drug class	Mechanism of prolonged QT
Antiarrhythmic: Class IA (quinidine, procainamide)	Blocks outward K ⁺ currents and inward Na ⁺ currents ^{1–3}
Antiarrhythmic: Class III (dofetilide, ibutilide, sotalol, amiodarone)	Strong IKr blockers that prolong QTc in a dose-dependent manner ^{1–3}
Antimicrobial: macrolides, fluoroquinolones	IKr blockers. Sparfloxacin withdrawn from the US market in 2000 due to risk of arrhythmias ¹
Antipsychotic: phenothiazine, thioridazine, chlorpromazine, haloperidol	IKr blockers ¹
Promotility: Cisapride	IKr blockers, high affinity. Cisapride withdrawn from the US market in 2000 due to risk of arrhythmias ¹
Antimalarial: chloroquine, halofantrine	Strong IKr blockers. TdP risk highest with halofantrine ^{1,5}

IKr: delayed rectifier potassium current

TdP: torsades de pointes

quinine, and some physicians will continue to prescribe it, as there are few alternative treatments for nocturnal muscle cramps.

CONCLUSIONS

The present case is illustrative of classic etiologies and findings of ALQTS. This patient had several risk factors for QT prolongation, including her gender, age, hypokalemia, left ventricular hypertrophy, bradycardia, and perhaps enhanced autonomic tone owing to her bouts of vomiting. She was extremely fortunate that her PMVT was non-sustained and did not degenerate into ventricular fibrillation. With her constellation of myriad contributors, she could have just as easily had permanent side effects or even died. She also serves as an important reminder for providers to take a complete medication history, especially prior to new prescriptions, including the use of duplicative and alternative medications (e.g., quinine sulfate for leg cramps) and type of alcohol consumption. We have included a few representative examples of common QT-prolonging drugs and their mechanism in Table 1. However, providers should also refer to the website CredibleMeds.org (formerly QTdrugs.org),¹⁷ which maintains an updated list of new drugs and interactions known to contribute to ALQTS, and also illicit drugs (e.g., cocaine) and over-the-counter medications (e.g., famotidine).

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Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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