Quinine Syncope Diagnosed by Life Vest
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Abstract
We present the case of a patient with ischemic cardiomyopathy using quinine as a remedy for leg cramps. A wearable cardioverter defibrillator (WCD) (LifeVest, Zoll Medical Corporation) recorded a sustained episode of polymorphic ventricular tachycardia resulting in syncope. Electrolyte concentrations were normal while QT interval was prolonged which improved after cessation of quinine and grapefruit juice.

Introduction
Ventricular arrhythmias are an important cause for morbidity and mortality in patients with cardiomyopathy (EF<35%). Wearable and implantable cardioverter defibrillators impart a final degree of protection but are associated with significant patient discomfort and morbidity. QT interval prolongation has been identified as a risk factor for precipitating ventricular arrhythmias. Due to presence of co-morbidities patients are often on multiple medications that can affect the QT interval, in addition several over the counter (OTC) medications have a similar effect. Drug interactions and even dietary interactions assume greater significance for these at risk individuals.

Case Presentation
A 66-year old Caucasian male was admitted through the emergency room (ER) after he received a shock from an external wearable defibrillator (LifeVest, Zoll Medical Corporation). He recalled that he was sitting on the commode when he felt dizzy and passed out, woke up on the floor with the conductive gel from the “LifeVest” all over his chest. There were no obvious physical injuries and he denied bladder or bowel incontinence. There were no reports of chest pain. He reported drinking significant amounts of “tonic water” (containing quinine) in place of water over the last week for leg cramps. He also mentioned continued regular use of grapefruit juice for several months.

Nine months prior to this presentation he had undergone coronary artery bypass grafting, three weeks prior to the current episode he underwent staged percutaneous coronary intervention (PCI) to saphenous vein graft to obtuse marginal 1 and protected left main coronary artery. He had been on aspirin, prasugrel, carvedilol, lisinopril, atorvastatin and furosemide. Echocardiogram done prior to PCI revealed a severely decreased left ventricular (LV) ejection fraction (EF 30%). He was fitted with a wearable defibrillator (LifeVest, Zoll Medical Corporation) approximately two weeks prior to current presentation.

In the ER LifeVest was interrogated and wave form analysis yielded an episode of sustained polymorphic ventricular tachycardia that lasted 34 seconds at a maximum rate of 286/min. Corrected QT interval (QTc) interval prior to initiation of ventricular tachycardia was 516 msec (corrected for right bundle branch block RBBB 476 msec) (Figure 1). The ventricular arrhythmia terminated spontaneously followed by an irregular slowly bradycardiac rhythm likely atrial fibrillation with slow ventricular rate and a maximal pause of 5.8 seconds. The patient eventually received a committed shock of 150 joules (Figure 2) as per device algorithm 16 sec after termination of ventricular tachycardia (VT) subsequently normal sinus rhythm at 78 beats per min was restored. Device algorithm included VT detection at 150/ min, ventricular fibrillation (VF) detection at 200/min while response time for VT was set at 60 seconds and for VF at 25 seconds. Although VT episode terminated spontaneously, background artifact/atrial fibrillation was gained up by the device (Zoll LifeVest) and interpreted as VF, which was eventually treated with a 150-joule shock.

An EKG on presentation revealed normal sinus rhythm with right bundle branch block and corrected QT (QTc) interval of 481 msec (corrected for RBBB 451 msec) (Figure 3). Laboratory evaluation was within normal limits with Potassium 3.9 mmol/L (normal values 3.5-5.0 mmol/L) and Magnesium 2.0 mg/dl (normal values 1.8-2.4 mg/dl). Troponin-I was 0.08 ng/ml (normal values 0.00-0.05) and subsequently trended down. An older EKG available revealed RBBB with a QTc of 460 msec (corrected for RBBB 430 msec).

Telemetry analysis over the next 48 hours did not reveal any arrhythmias and subsequent EKG showed normalization of QTc interval. The episode of polymorphic ventricular tachycardia was ascribed to ingestion of quinine, with concomitant intake of grapefruit juice that lead to inhibition of metabolism of quinine and subsequent toxicity with QTc prolongation and Torsades de Pointes. Patient was counseled against use of tonic water or any quinine containing supplement, as well as grapefruit juice prior to discharge. Follow up at 3 months revealed no further arrhythmias, and a repeat echocardiogram revealed improved LV function with EF 50-55%. LifeVest was discontinued at that time and the patient was followed up without any symptoms or events thereafter.

Discussion
Quinine has anti-malarial and curare like effects on muscle cells [1]. In addition to being used as an anti-malarial, it has been used for nocturnal leg cramps and restless leg syndrome. This “off label” use of quinine has continued despite FDA warnings [2]. Tonic water was used in the past as prophylaxis for malaria, its use has continued more for its distinctive bitter flavor. The ingredients in tonic water include Carbonated Water, High Fructose Corn Syrup, Citric Acid, Sodium Benzoate (preservative) and Quinine (Schweppes®) along with different flavors. FDA regulations limit the amount of quinine in tonic water to 83 ppm (83mg per liter), which continues to be used for leg cramps as an over the counter/home remedy. An 8-ounce serving of tonic water thus contains about 20 mg of quinine. Tonic water is marketed

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Received March 06, 2015; Accepted April 09, 2015; Published April 15, 2015


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torsades de pointes after ingesting tonic water and grapefruit juice for polypedia due to uncontrolled diabetes [13]. Grapefruit juice contains the flavonoid Naringin that inhibits CYP3A4 [14] of the cytochrome P450 complex inhibiting the metabolism of quinine and increasing its plasma concentration. The inhibition of CYP3A4 by grapefruit juice is concentration dependent with low concentrations inhibiting intestinal enzyme while the hepatic enzyme is inhibited at higher doses [15]. Interestingly quinidine can cause torsades at low sub therapeutic concentrations and not necessarily at higher concentrations [16]. The QTc prolonging effect of outward potassium channel (IKr) blockade is likely offset by the sodium channel blockade at higher doses [17]. Selzer and Wray first introduced the term quinidine syncope in 1964 when they described a series of patients that had syncope due to polymorphic ventricular tachycardia while being treated for atrial arrhythmias with quinidine [18]. This was mainly seen at lower concentrations and the arrhythmias were self-limited.

A wearable cardioverter defibrillator (WCD) is an external device by different companies in the market e.g. Canada Dry, Schweppes etc. In the past dose of quinine used for leg cramps was 300 mg at bedtime.

Quinine and Quinidine are stereoisomers with a bioavailability of 70-90% after enteral administration. Onset of action of Quinine is about 30 minutes while peak serum levels are achieved in 1-3 hours based on the preparation used [3]. In the serum Quinine is tightly bound to serum α1-acid glycoprotein [4]. Quinine is metabolized through hepatic CYP3A4 system with a half-life of about 11 hours [5]. Quinine and quinidine have similar anti-malarial and cardiac effects although the anti-arrhythmic effects are more pronounced for the latter [6,7]. Mechanism of action involves blocking of inward sodium current (INa), which delays the rate of rise of action potential upstroke (phase 0) and prolongs action potential duration. QTc prolongation is seen with both quinine and quinidine (more pronounced) due to blockade of IKr channel responsible for delayed rectifier outward potassium current [8]. Cardiovascular effects also include slowed sinus discharges and slowed AV node conduction [9,10]. In fact quinine and quinidine have been successfully used interchangeably as anti-arrhythmic and anti-malarial respectively. The easy availability of quinine supplements and its use as an herbal/home remedy for leg cramps can lead to dangerous consequences due to its effects on the cardiovascular system. Polymorphic ventricular tachycardia has been reported with concomitant use of astemizole and quinine [11] as well as co-administration with digoxin [12]. In addition to interactions with pharmacologic agents, effect of diet on quinine metabolism has also been shown to be clinically significant. Hermans et al. reported a patient with long QT syndrome that presented with resistant
worn by the patient that continuously monitors the rhythm. WCD uses heart rate, template matching and event persistence, utilizing algorithms to determine whether defibrillation is warranted, this is followed by a series of vibratory and audible alerts for the patient to abort the defibrillation attempt if patient is hemodynamically stable. WCD is indicated for patients at high risk for sudden cardiac death (SCD) until they become eligible for an implantable cardioverter defibrillator (ICD) or the risk of SCD is mitigated.

Clinical trials like wearable defibrillator investigative trial (WEARIT) and Bridge to ICD in patients at risk of arrhythmic death (BIROAD) trials as well as post marketing analysis have shown a high rate of appropriate detection and treatment of tachyarrhythmias in at risk populations [19,20].

VALIANT (valsartan in acute myocardial infarction) trial showed that risk of SCD post-acute myocardial infarction is maximal during the first 30 days [21].

Conclusion

Our patient with a recent non ST elevation MI, subsequent revascularization and transient LV dysfunction was at high risk for ventricular arrhythmias. Intentional co-ingestion of quinine and grapefruit juice disrupted the metabolism of quinine and precipitated the episode of polymorphic ventricular tachycardia. Although the ventricular tachycardia episode was self-limited, the background arrhythmia should have their medication profile scrutinized for those with inherited channelopathies predisposing to ventricular arrhythmias. Intentional co-ingestion of quinine and grapefruit juice disrupted the metabolism of quinine and precipitated the episode of polymorphic ventricular tachycardia. Although the ventricular tachycardia episode was self-limited, the background arrhythmia should have their medication profile scrutinized for those with inherited channelopathies predisposing to ventricular arrhythmias. Intentional co-ingestion of quinine and grapefruit containing Naringin can have disastrous consequences. The concentration of quinine in tonic water is small but coupled with presence of inhibitors of metabolism of quinine like grapefruit containing Naringin can have disastrous consequences.

People at risk for SCD including those with cardiomyopathy and those with inherited channelopathies predisposing to ventricular arrhythmias should have their medication profile scrutinized for any potential interaction that can cause QTc prolongation. Over the counter medications and herbal therapies also need to be looked into when caring for these patients and they should be educated about the possible interactions with over the counter and herbal therapies prior to discharge.

References