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### **Authors**

Feng, Zekun

Press, Marcella A

Buch, Eric F

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## CLINICAL VIGNETTE

# Antiarrhythmic Medications, Acquired Long QT Syndrome, and Torsades de Pointes

Zekun Feng, PharmD, MD, Marcella A. Press, MD, PhD, and Eric F. Buch, MD

### Background

Acquired long QT syndrome (LQTS) is typically iatrogenic. Over 100 medications are known to cause QT prolongation, usually by affecting cardiac potassium channels. The most commonly implicated drugs include certain antiarrhythmic, psychotropic, and antimicrobial medications.<sup>1,2</sup> In addition, electrolyte derangements such as hypomagnesemia, hypokalemia and hypocalcemia can also result in acquired LQTS.

The QT interval reflects the time needed for ventricular repolarization, and it is inversely related to heart rate. Multiple formulas have been developed to correct the QT interval for heart rate.<sup>3-5</sup> Bazett's formula ( $QT_c = QT/\sqrt{RR}$ ) is commonly used to calculate  $QT_c$ , but correction may be less accurate at heart rate extremes.<sup>6</sup> Furthermore, the QT interval includes the QRS complex, and is thus affected by abnormalities of depolarization that affect QRS duration, such as bundle branch block. Multiple formulas have been proposed to correct for QRS abnormalities.<sup>7-9</sup>

The threshold for prolonged QT interval differs by age and gender, but is typically defined as corrected QT interval ( $QT_c$ ) >440 milliseconds (ms) in male adults and  $QT_c$  >460 ms in female adults. Patients with  $QT_c$  >500 ms are at increased risk for Torsades de pointes (TdP), a form of polymorphic ventricular tachycardia characterized by alternating QRS axis and morphology around the isoelectric baseline.<sup>10</sup> The name is derived from French for "twisting of the points". TdP is usually self-limited but may degenerate into life threatening ventricular fibrillation or rarely monomorphic ventricular tachycardia.<sup>10</sup> The treatment of prolonged TdP is focused on maintaining hemodynamic stability, correcting contributing factors, and preventing recurrence. We present a case emphasizing the effects of antiarrhythmic medications on a patient with acquired LQTS that degenerated into TdP.

### Case Presentation

A 72-year-old male with myelodysplastic syndrome receiving chemotherapy, complicated by pancytopenia and neutropenic fever, was ultimately diagnosed with biopsy-confirmed Sweet syndrome. He was taking levofloxacin and fluconazole for neutropenic prophylaxis for 5 days before returning to the emergency department with fevers and malaise. Initial vital

signs were significant for temperature of 103.2 F and sinus tachycardia at 119 beats per minute. Initial labs showed serum potassium of 4 and lactate of 40. He received 3 liters of intravenous (IV) fluid and was given IV meropenem, vancomycin, and metronidazole. During a full body CT scan, the patient began having bursts of polymorphic ventricular tachycardia with rates up to 240 beats per minute. However, blood pressure was stable at 110/70, and he was asymptomatic from the arrhythmia. He was given 2 grams of IV magnesium, but the episodes continued. Next he received 500 milligrams of IV procainamide over 30 minutes. Interestingly, the rhythm converted to monomorphic ventricular tachycardia at 250 beats per minute after procainamide, but he remained hemodynamically stable. Cardiology was consulted, and since he was not bradycardic, he was recommended to receive lidocaine rather than isoproterenol or temporary pacing. After receiving a 100 milligram bolus of IV lidocaine, ventricular arrhythmias ceased and he remained in sinus tachycardia. After review of the admission electrocardiogram, patient was noted to have  $QT_c$  of 510 prior to the TdP events, in the setting of recent levofloxacin and fluconazole use. Telemetry strips show that TdP events were initiated by premature ventricular contractions (PVCs) occurring before the end of the T wave (R on T phenomenon).

### Discussion

This case highlights the following teaching points. 1) Medication-induced acquired LQTS; 2) Class I/III antiarrhythmic medications and QT interval; 3) Reverse use dependence versus use dependence; 4) Immediate and long-term management of TdP; 5) Effect of procainamide and lidocaine on this patient with TdP.

In addition to QT prolonging medications and electrolyte abnormalities, bradyarrhythmias and underlying heart disease also increase the risk of developing acquired LQTS and deterioration to TdP. There is typically a clear temporal relationship with medication-induced LQTS/TdP, with events occurring several days after initiation of the offending medication. Medication-induced TdP is usually pause dependent, with an initial PVC followed by a supraventricular complex and further QT prolongation, and a second PVC starting off the TdP, often referred to as a "long-short sequence."<sup>2,10</sup> When triggered activity causes PVC during phase 2 or 3 of the action

potential, it is called an early after-depolarization (EAD), and can cause R on T phenomenon that initiates TdP.

Class III and, to a lesser extent, Class IA antiarrhythmic medications block the repolarizing potassium channels and outward IKr current, leading to a prolonged QT interval and increased risk for TdP. Class III agents, including sotalol, dofetilide, ibutilide, and amiodarone, all markedly prolong the QT interval. However, amiodarone alone is rarely associated with TdP, with estimated overall incidence of less than 1 percent.<sup>11,12</sup> This can be explained by its concomitant calcium channel and beta blockade, and lack of QT dispersion.<sup>10,12</sup> Quinidine, one of the oldest class IA antiarrhythmics, has fallen out of favor due to its proarrhythmic side effects. "Quinine syncope", likely due to acquired LQTS and self-terminating TdP has been reported in 1.5 percent of patients per year.<sup>9</sup> This can even occur with low to normal quinidine plasma levels.<sup>9</sup> Procainamide, another class IA agent, prolongs the QT interval in proportion to its plasma levels. Its active metabolite N-acetylprocainamide (NAPA) has potassium channel blocking activity and contributes to QT prolongation. Lidocaine and mexiletine are class IB agents, which decrease refractory period and shorten the QT interval. Lidocaine has been reported to be a potential treatment for drug-induced TdP.<sup>9,13</sup> Class IC agents, including flecainide and propafenone, do not affect repolarization or QT interval. However, by slowing conduction they increase risk of reentrant ventricular arrhythmias in patients with structural heart disease.

Use dependence means that an antiarrhythmic drug has more pronounced effects at higher heart rates, while reverse use dependence means that it has weaker effects at higher heart rates. Class IB and IC antiarrhythmic drugs exhibit use dependence, while class IA and III agents show reverse use dependence. The difference results from each medication's intrinsic activity at different heart rates. Use dependence is seen in sodium channel blockers with high affinity for channels in the active state, resulting in increased drug binding and enhanced effect during higher heart rates. Reverse use dependence is seen in potassium channel blockers, which preferentially interact with receptors in the resting state. This causes increased prolongation of action potential duration and ventricular refractoriness at lower heart rates, which increases vulnerability to EAD and TdP at slower heart rates. Despite being a class III antiarrhythmic medication, amiodarone does not exhibit reverse use dependence; its effects on action potential duration are similar at different heart rates due to its additional receptor blocking properties.

It is important to understand the rationale behind immediate and long-term management of TdP. Immediate management focuses on hemodynamic stabilization and termination of the arrhythmia. Magnesium sulfate 2 grams IV push should be given immediately, along with withdrawal of offending agents and potassium correction. Repeat magnesium boluses can be given if the patient does not respond. Unsynchronized cardioversion can be used for unstable or prolonged cases. As discussed earlier, lidocaine can be successfully used since class IB antiarrhythmics shorten the QT interval. Class IA and class III antiarrhythmics prolong the QT interval and should be avoided. This is true of amiodarone as well; even though it rarely causes TdP, it should not be considered a treatment for

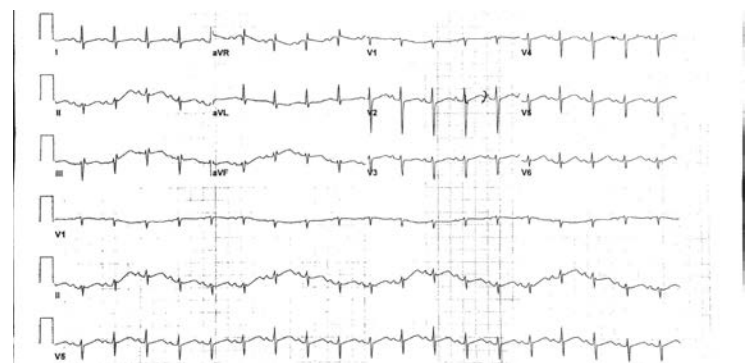
this arrhythmia, and is likely to worsen the situation by further prolonging the QT interval. One effective method of shortening the QT interval in bradycardic patients is to raise the heart rate by administering IV isoproterenol or placing a temporary transvenous pacemaker. In a review of the above treatment options, 19 of 19 patients had TdP terminated with cardioversion, 9 of 9 with pacing at heart rate of 100 to 120, 5 of 6 with isoproterenol, but only 7 of 14 with Lidocaine.<sup>9</sup> Long-term treatment focuses on avoiding factors that might prolong the QT interval to prevent recurrence and sudden death. Underlying causes of acquired LQTS should be identified, and QT-prolonging medications should be avoided whenever possible. If the etiology of LQTS cannot be identified or mitigated, oral beta-blockers and permanent pacemaker and/or cardioverter-defibrillator can be considered.<sup>8,14</sup> Family members may also be screened for congenital LQTS.

In summary, our patient with recent use of levofloxacin and fluconazole presented with medication-induced LQTS. He deteriorated into TdP initiated by PVCs and received magnesium without effect. The subsequent use of procainamide appears to have converted the rhythm from TdP into monomorphic ventricular tachycardia. The use of lidocaine in our case converted patient's rhythm back to sinus, which is consistent with the published literature. If the patient had become hemodynamically unstable or had sustained TdP, unsynchronized cardioversion would have been the next best option. In the future, this patient will avoid QT-prolonging medications.

## Conclusion

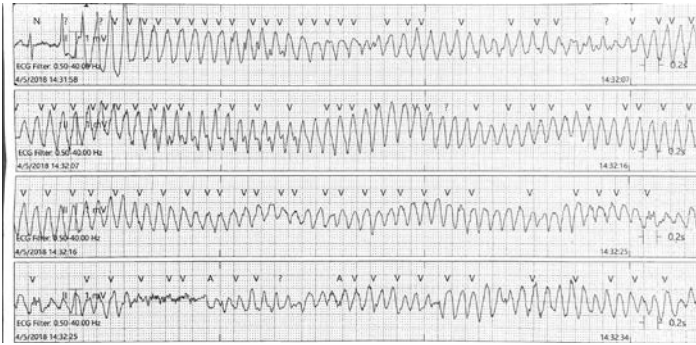
Acquired LQTS is often caused by medications and electrolyte abnormalities. Risk for TdP is increased with combination of multiple factors. Class IA and III antiarrhythmic medications affects potassium channels thus prolonging QT interval, and should be avoided in patients with preexisting QT prolongation. In addition, Class IA and III agents besides amiodarone exhibit reverse use dependence and increased risk for TdP at low heart rates. Management of TdP focuses on hemodynamic stabilization and prevention of recurrence.

**Figure 1:**  
Initial ECG on admission showed prolonged QTc of 510 before the Torsades de Pointes (TdP) event.



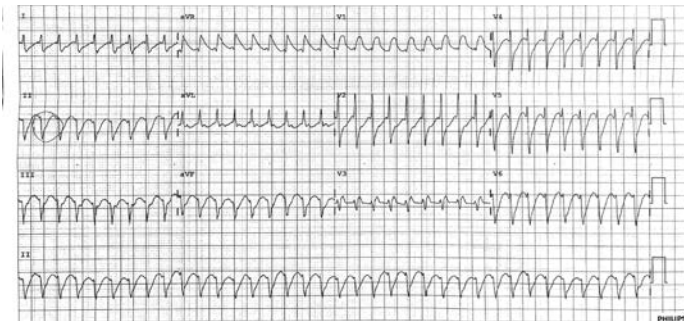
**Figure 2:**

Premature ventricular contraction (PVC) initiated R on T phenomenon leading to TdP.



**Figure 3:**

Rhythm conversion to monomorphic ventricular tachycardia after administration of procainamide.



**Figure 4:**

Conversion to sinus rhythm after administration of lidocaine.



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