Amiodarone-induced torsades de pointes in a patient with HIV on combination antiretroviral therapy

Fahad Alsindi, Cliona Murphy and David Martin

Department of Medicine, Lahey Clinic Medical Center, Burlington, MA, USA

Corresponding address: David Martin, MD, FRCP, FACP, Cardiac Arrhythmia Service, Lahey Clinic, 41 Mall Road, Burlington, MA 01801, USA.

Email: david.t.martin@lahey.org

Abstract

A case of prolongation of the QT interval and associated life-threatening ventricular arrhythmia is presented. The particular features of this case include HIV positivity, acute coronary ischemia, and treatment with drugs known to increase QT interval. The relationship between these potential causes is analyzed and discussed. This is the first report of such a complication of combined therapy with amiodarone and antiretroviral medication.

Keywords

Acquired long QT; torsades de pointes; ventricular fibrillation; drug interaction; highly active antiretroviral therapy.

Background

Long QT syndrome (LQTS) is a condition characterized by abnormal ventricular repolarization as a result of abnormal potassium or sodium cardiac ion channel currents. LQTS can be either inherited or acquired and is associated with malignant ventricular arrhythmias, classically torsades de pointes (TdP).

Acquired LQTS reflects conditions under which a number of heterogeneous causative factors including drugs, metabolic disturbances (particularly hypokalemia and hypomagnesemia), or acute illness, lead to abnormal cardiac channel fluxes and prolonged repolarization. Drugs are the most common causes of acquired LQTS, including several antibiotics, antiarrhythmics and antidepressants.

We report a case of drug-induced acquired LQTS complicated by TdP with cardiac arrest in a patient receiving a combination of antiretroviral therapy and amiodarone. Such a complication of this drug combination has not been described previously.

Clinical presentation

A 53-year-old HIV-positive woman presented with chest pain and dyspnea. An electrocardiogram (ECG) showed inferolateral ST segment depression. Troponin I was increased at 10 ng/ml and non-ST elevation myocardial infarction was diagnosed. Her background history included diabetes...
mellitus, hyperlipidemia, hypertension and HIV infection for 15 years. She was taking highly active antiretroviral therapy (HAART) in the form of abacavir 300 mg twice daily, lamivudine 150 mg daily, darunavir 600 mg twice a day, raltegravir 400 mg once a day. She complained of previous palpitations but denied syncope. Her family history was negative for sudden cardiac death.

On admission, the ECG showed ischemic changes with a QTc interval of 459 ms (Fig. 1) (normal <460 ms). Echocardiogram revealed impaired left ventricular function of 30–35% and significant mitral regurgitation. Coronary angiography revealed significant triple vessel disease and she subsequently underwent 4-vessel coronary artery bypass grafting and mitral valve replacement. Postoperatively she was started on metoprolol 12.5 mg orally twice daily and amiodarone 200 mg orally twice daily as prophylaxis against atrial fibrillation.

On postoperative day 5 she had a cardiac arrest in the setting of TdP. Fig. 2 shows the classic long/short/long ventricular sequence seen in LQTS before arrhythmia onset. Cardiopulmonary resuscitation and a 200-J shock restored sinus rhythm and hemodynamic stability. She was given an amiodarone bolus of 300 mg intravenously, followed by a 24-h infusion. She was re-intubated. Her electrolytes were within normal limits. Cardiac biomarkers were negative and the ECG showed no new ischemic changes. Nine hours following intravenous amiodarone administration, her QTc interval was 613 ms, using the Bazett formula. In view of this, amiodarone and antiretroviral medications, agents known to prolong the QT interval, were discontinued. The following day she had a further episode of TdP again requiring an emergency DC shock. The QTc interval remained prolonged at 674 ms (Fig. 3). She was extubated on postoperative day 8. By the 10th postoperative day the QTc had almost normalized at 464 ms. She underwent defibrillator implantation for secondary prevention. Following this, antiretroviral medications were restarted and she was subsequently discharged without further complication. Follow-up 10 days after discharge showed normalization of the ECG. At 6-month follow-up the patient was alive and well and had experienced no defibrillator discharges.

![Fig. 1. ECG on admission (QTc=459 ms).](image)

![Fig. 2. Short-long-short ventricular intervals followed by TdP degenerating into ventricular fibrillation.](image)
Discussion

This case describes the first known report of acquired LQTS and TdP cardiac arrest in the context of combined use of amiodarone with antiretroviral agents. Our patient was doing well for the first 5 days after coronary artery bypass graft surgery and there was no evidence to suggest an early ischemic insult or graft occlusion. Although she did have depressed cardiac function, which can herald ventricular arrhythmias, the ECGs after arrest clearly suggested QT prolongation as a likely contributor or principal cause of the cardiac arrest.

The patient did not have LQT before the administration of amiodarone. It is the practice of our institution to start amiodarone and beta-blockers after cardiac surgery. This practice is influenced by randomized controlled studies showing decrease in the incidence of postoperative atrial fibrillation and length of hospital stay\cite{1,2}.

The time course of LQT and TdP in this patient suggests that no single drug was responsible and it is likely that the combination of amiodarone with the patient’s antiretroviral medication led to the QT interval prolongation.

Drug-induced LQTS: mechanisms

The pathophysiology of LQTS is derangements in cardiac ion flow. Three ionic mechanisms could lead to increased repolarization: (1) activation of delayed Na current can occur early in repolarization and has been implicated in ibutilide QT prolongation\cite{3}; (2) increase in inward Ca\textsuperscript{2+} current; (3) most drug-induced QT prolongation is due to a reduction in or blockade of the rapid delayed rectifier current (\(I_{Kr}\)) resulting in prolonged cardiac repolarization\cite{4}. This leads to activation of inward depolarization current of (\(I_{Ca-L}\) and \(I_{Na}\))\cite{5}. This generates early afterdepolarizations and may initiate triggered activity at the end of repolarization. In a favorable myocardial substrate this may induce re-entry and provoke TdP.

Amiodarone and acquired LQTS

Amiodarone is a class III antiarrhythmic that blocks cardiac potassium channels. Therefore slight prolongation of the QT interval, which is usually not clinically significant, can be normally seen in addition to its therapeutic effects. It is metabolized by CYP3A4. Although QT prolongation has been noted in up 20% of patients in one series\cite{6}, the incidence of TdP in the setting of amiodarone use has been documented to be as low as 0.7%\cite{7,8}.

Acute management of TdP

Immediate cardioversion should be instituted in the event that hemodynamic compromise ensues or when TdP does not self-terminate. After restoration of sinus rhythm, the next priority is to prevent recurrences. This is done by withdrawal of the offending agents, in this case amiodarone and antiretrovirals. Serum electrolytes should be optimized. Temporary transvenous cardiac
pacing and isoproterenol are useful in the setting of bradycardia-dependent TdP, which is the most frequent scenario in drug-induced QT prolongation\[9\].

**Antiretrovirals and acquired LQTS**

Several antiretroviral drugs have been associated with acquired QT prolongation. In particular, the protease inhibitors (PI) may be the most important of these with a number of case reports noting prolongation of the QT interval and TdP in patients taking efavirenz, tenofovir, and abacavir\[10,11\]. Studies have also examined QT intervals in patients on a combination of antiretrovirals. In one study, patients taking combination therapy of nelfinavir with azido thymidine (AZT) had a threefold higher risk of QTc prolongation compared with the nelfinavir group alone\[12\]. Such findings have important implications for the safe use of modern day combination HIV therapy.

Our patient was receiving a combination of a PI, integrase inhibitor, and two nucleoside reverse transcriptase inhibitors (NRTIs). Abacavir and lamivudine are both NRTIs and are metabolized via the cytochrome P450 system. QT prolongation has not been associated with these drugs.

Raltegravir is the first in its class of oral integrase inhibitors. It is metabolized by the UGT1A1-mediated glucuronidation pathway and in vivo is not metabolized via the CYP450 pathway. This drug appears to have no noticeable effect on the QT prolongation\[13\].

Daranavir is a PI that is metabolized predominantly in the liver via the CYP450 pathway\[14\]. Darunavir has the longest elimination half-life of 15 hours\[15\]. Pharmacodynamic mechanisms governing the metabolism of this drug have important interactions with other drugs that use this metabolic pathway. These include antimicrobials, antihistamines, psychotropic drugs, and antiepileptics. Factors such as age, sex, liver disease, and co-administered hepatic enzyme inhibitors, condition the activity of CYP450 and toxicity profile of antiretrovirals\[14\].

PIs are potent inhibitors of CYP3A4, a metabolic pathway that biotransforms 60% of oxidized drugs and is important in the metabolism of a multitude of drugs\[16\]. This would permit increased tissue levels of other QT-prolonging drugs and augment the risk of TdP. PIs also directly inhibit the (HERG) gene coding for rapid delayed rectifier potassium channel thereby resulting in QT prolongation and TdP\[4,17\].

**Amiodarone/antiretroviral combination**

It is clear that individually, amiodarone and antiretrovirals can increase the QTc interval. In this case, given that the QTc began to normalize 5 days after discontinuing these agents, when amiodarone would likely still be present in the tissues, we considered that amiodarone was not the sole agent responsible for QT prolongation. Indeed, removal of the HIV medication led to QTc normalization within 5 days, consistent with the elimination half-lives of raltegravir and darunavir. Amiodarone rarely causes TdP, however this case suggests that if it is used in combination with antiretrovirals, LQTS and TdP can occur.

Antiretroviral therapy increases serum concentrations of amiodarone. This interaction is mediated via CYP3A4. Thus CYP3A4 inhibition would potentiate QT prolongation via two mechanisms. The first is by drug-to-drug interaction. In our case, darunavir would inhibit CYP3A4 dependent metabolism of amiodarone and would promote its toxicity. This has been classified as FDA Risk Category X\[18\]. The other mechanism of QT prolongation with HIV PIs is a dose-dependent blockade of HERG channels. Lopinavir has been shown to block the repolarizing potassium (\(I_{Kr}\)) current in neonatal mouse cardiac myocytes\[19\].

**HIV and LQTS: direct viral effects**

The patient’s HIV history may be an important component. It is estimated that around 6–7% of HIV-positive patients have myocardial disease\[20\]. HAART has a number of cardiotoxic effects that can lead to dilated cardiomyopathy and accelerated atherosclerosis\[21,22\]. HIV represents an independent risk factor for QT prolongation. In a retrospective analysis, there was a fourfold increase in QT interval in hospitalized HIV patients compared with hospitalized non-HIV patients\[23\].

**Acquired LQTS: individual predisposition**

That certain individuals are more susceptible to acquired LQTS than others is suggested by the Multiple Hit Hypothesis, where multiple dynamic factors in an individual contribute to acquired
QT prolongation and the occurrence of TdP\cite{5}. Within this hypothesis there may be a role for the HERG gene (also known as the KCNH2 gene) which encodes the rapid rectifier current ($I_{Kr}$) potassium channel protein\cite{4}. Subclinical mutations of this gene with incomplete penetrance can occur, with affected individuals having a reduced repolarization reserve. It is known that mutations in $I_{Kr}$ and $I_{Ks}$ have been implicated in congenital LQTS. Blockage of the rapid rectifier current ($I_{Kr}$) has been implicated in most cases of QT prolongation caused by drugs\cite{24}.

Repolarization reserve refers to the redundancy that is maintained when one of the $I_{K}$ currents are lost. Repolarization reserve also extends beyond the singularity of inhibition of $I_{Kr}$ or lack of genetic expression. Genetic testing was not performed on our patient, but patients who develop acquired LQTS may have a preexisting subclinical congenital LQTS that is unmasked by offending agent(s)\cite{4,5}.

**Teaching point**

This case highlights an important and potentially lethal drug interaction. This is the first known report of acquired LQTS and TdP cardiac arrest in the context of combined use of amiodarone with certain antiretroviral agents.

It is important for health care providers to consider the risk of QT prolongation in patients with HIV on antiretroviral therapy. This is of additional importance when a new medication with documented potential for QT prolongation is commenced in this patient population. There is a need for close monitoring of QT interval, serum electrolytes, and co-administered drugs in patients at risk of QT prolongation.

**References**


