QT interval prolongation: Life-threatening consequences of life saving drugs

Sumit K Shah*
Department of Pathology, University of Arkansas for Medical Sciences. Little Rock, AR, USA

Abstract

Acquired long QT syndrome is a frequent phenomenon in clinical practice. QT interval prolongation can lead to fatal ventricular arrhythmias and even sudden cardiac death. Adverse effect from pharmaceuticals is the most common reason for QT interval prolongation and also for withdrawal of marketed drugs. Critically ill hospitalized patients often receive multiple drugs with proarrhythmogenic properties making them susceptible to QT interval prolongation. Seropositive patients are also very susceptible to QT interval prolongation because of concurrent use of protease inhibitors with proarrhythmogenic properties. Hepatic and renal dysfunctions are major contributing factors for QT interval prolongation. Reduced drug metabolism due to hepatic dysfunction and reduced drug clearance due to renal functional impairment can propel electrocardiographic abnormalities. Other contributing factors are advanced age, female sex, occult genetic predisposition for long QT syndrome, electrolyte imbalance, and underlying cardiovascular disorders. Patients at high-risk of developing QT interval prolongation should be approached with caution. While in certain situations it is mandatory to administer drugs with proarrhythmogenic properties, it is also important to continuously monitor the high-risk patients with EKG to prevent worsening of QT interval prolongation.

Abbreviations: LQTS: Acquired Long QT Syndrome; MS: Milli Seconds; EKG: Electrocardiogram; AHA: American Heart Association; CYP4503A: Cytochrome P4503A; SVQ: Saquinavir; RTV: Ritonavir

Introduction

Acquired long QT syndrome (LQTS) is undeniably more frequently encountered in clinical practice as compared to congenital LQTS [1]. Pharmaceutical drugs are by far the most frequent variable causing acquired LQTS [2]. Drug-induced LQTS is also the most common reason for withdrawal of marketed drugs [1]. The pharmaceutical industry has advanced tremendously in the past couple of decades revolutionizing treatment in the contemporary times [3]. But the advent of more efficacious therapeutic drugs has also led to an increase in the incidence of complications due to drug-induced adverse effects [4]. Prolonged QT interval is a precursor for fatal arrhythmias such as polymorphic ventricular tachycardia and Torsades de Pointes (TdP), which can eventually lead to sudden cardiac death [5]. According to the leading experts, QT interval ≥ 460 milliseconds (ms) in women and QT > 450 ms in men is considered as prolonged QT interval [6]. The risk of torsades de pointes (TdP) increases by two to three-fold for patients with QT interval > 500 ms. Additionally, there is an approximate 5-7% exponential increase in the risk of developing ventricular arrhythmias for every 10 ms increase in QT interval duration. Acquired LQTS can potentially increase hospital stay and can even increase the all-cause mortality [7]. Fatal ventricular arrhythmias and sudden cardiac death is a major public health issue for healthcare providers [1].

Contributing factors

The most common potential reason for electrocardiogram (EKG) abnormalities in hospitalized patients is administration of drugs with proarrhythmogenic properties. A study was conducted on 501 cardiac ICU patients to gain a more precise understanding of this association. Electrocardiographic monitoring revealed that almost 37% (n = 187) of those hospitalized patients experienced QT interval prolongation. It was reported that the drugs most frequently administered to those patients were ondansetron, amiodarone, metronidazole, and haloperidol and QT interval prolongation in this cohort might be due to individual drug effect or drug-drug interaction [8]. Critically ill patients are often treated with multiple proarrhythmogenic drugs that can considerably increase the risk of developing LQTS [9]. American Heart Association (AHA) recommends periodic EKG monitoring for patients receiving QT interval-prolonging drugs [10]. Pickham (2010, pp 572-576) reported data collected from 154 patients admitted to 5 critical care units. Out of those 154 patients, 24% patients exhibited prolonged QT interval during their period of hospitalization [10]. It was concluded that critically ill patients are at high-risk of developing LQTS and they should be carefully evaluated and periodically monitored with EKG. Drug classes and names of drugs with proarrhythmogenic properties are listed in table 1 [11].

Seropositive patients on highly active antiretroviral treatment (HAART) may also be very susceptible to developing acquired LQTS. Highly active antiretroviral medications, especially protease inhibitors (PIs), are potent inhibitors of cytochrome P4503A (CYP4503A) enzyme. Cytochrome P4503A metabolizes a wide variety of drugs in the body [12] and concurrent administration of drugs inhibiting CYP4503A can propel EKG abnormalities. Protease inhibitors such as Saquinavir (SVQ) and Ritonavir (RTV) are often used in combination

*Correspondence to: Sumit K Shah, Department of Pathology, Slot 845, University of Arkansas for Medical Sciences 4301 W Markham Street, Little Rock, AR 72205, USA, E-mail: SSUAH3@uams.edu

Key words: acquired long QT syndrome, prolonged QT interval, QT interval prolongation, sudden cardiac death, torsades de pointes

Received: September 17, 2018; Accepted: October 30, 2018; Published: November 02, 2018

Pharm Drug Dev Ther, 2018 doi: 10.15761/PDDT.1000109 Volume 3(1): 1-3
Shah SK (2018) QT interval prolongation: Life-threatening consequences of life saving drugs

### Table 1. Drugs with QT interval prolonging properties

| Class                              | Drug names                                                                 |
|------------------------------------|-----------------------------------------------------------------------------|
| Anti-arrhythmics                    | Sotalol, Amiodarone, Quinidine, Procainamide, Disopyramide, Flecainide, Dofetilide, Dronedarone |
| Diuretics, Anti-hypertensive        | Hydrochlorothiazide, Indapamide, Nicardipine (11), Furosemide (2)           |
| Anti-anginal                        | Ranolazine, Bepridil (11)                                                  |
| Anti-biotics                        | Moxifloxacin, Levofloxacin, Ofloxacin, Gatifloxacin, Ciprofloxacin, Erythromycin, Azithromycin, Clarithromycin, Trimethoprim-Sulfamethoxazole (11), Metronidazole (8) |
| Anti-fungal                         | Ketoconazole, Fluconazole, Itraconazole, Voriconazole (11)                  |
| Anti-viral                          | Ritonavir, Atazanvir (11), Saquinavir (14)                                  |
| Anti-emetics                        | Ondansetron, Granisetron, Dolasetron (11)                                  |
| Antihistamines                      | Diphenhydramine, Terbutaline, Astemizole (11)                               |
| Decongestants                       | Pseudoephedrine, Phenylpropanolamine (11)                                  |
| Bronchodilators                     | Albuterol, Salmeterol, Metaproterenol, Terbutaline, Levobuterol, Ephedrine (11) |
| Muscle relaxers                     | Tizanidine (11)                                                            |
| Nonsteroidal anti-inflammatory      | Diclofenac, Celecoxib, Ketorolac (18)                                      |
| Opiates                             | Methadone, Levemethadyl (11), Oxycodone, Tramadol (18)                      |
| Anti-depressants                    | Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram, Amitriptyline, Nortriptyline, Imipramine, Desipramine, Doxepin, Venlafaxine, Mirtazapine (11) |
| Anti-psychotics                      | Haloperidol, Thoridazine, Clozapine, Risperdone, Quetiapine, Chlorpromazine (11) |

### Conclusion

Drug-induced QT interval prolongation is a critical issue [18]. Drugs leading to fatal heart rhythm disorders should be prescribed with caution because life-saving drugs can also lead to life-threatening complications. Healthcare providers should be on guard for symptoms and signs such as syncope, near-syncope [19] and ventricular arrhythmias in hospitalized patients [20]. Critically ill patients are more susceptible to develop QT interval prolongation due to multiple comorbidities and coadministration of drugs with proarrhythmogenic properties. A recent study reported that 293 out of 41,649 hospitalized patients reported severe LQTS (QTc 529 ± 38 ms). All-cause mortality for this group was 32% after a follow-up of 255 ± 63 days. Also, symptoms and signs most commonly encountered in the study patients with prolonged QT interval were syncope and ventricular arrhythmias [21]. Another study was conducted on 900 patients admitted to a cardiac ICU. Of those, 166 patients already had a QT interval > 500 ms and yet they received QT interval-prolonging drugs [22]. Thus, patients on multiple drug regimens should be constantly evaluated with EKGs or telemetry to avoid fatal complications from worsening of QT interval prolongation [19]. QT interval prolongation can cause malignant arrhythmias and can eventually lead to sudden cardiac death if not addressed promptly [20]. Unfortunately, not all patients with LQTS may exhibit EKG abnormalities and their first presentation can be an unexpected death. Periodic EKG monitoring or telemetry can be of significant diagnostic and therapeutic importance because it can help detect and manage LQTS [23]. Elucidating the precise risk factors may also help in reducing the incidence of QT interval prolongation and by extension, reducing the incidence of fatal complications due to ventricular arrhythmias.

### References

1. Ramalho D, Freitas J (2018) Drug-Induced Life-Threatening Arrhythmias and Sudden Cardiac Death: A Clinical Perspective of Long QT, Short QT and Brugada Syndrome. Rev Port Cardiol 37: 435–446. [Crossref]
2. Fernandes FM, Silva EP, Martins RR, Oliveira AG (2018) QTc Interval Prolongation in Critically Ill Patients: Prevalence, Risk Factors and Associated Medications. PLoS One 13: e0199028. [Crossref]
3. Kramer SA, Adjei IM, Libhsetawar V (2015) Advancements in The Delivery of Epigenetic Drugs. Expert Opin Drug Deliv 12: 1501–1512. [Crossref]
4. Nachimuthu S, Assar MD, Schussler JM (2012) Drug-Induced QT Interval Prolongation: Mechanisms and Clinical Management. Ther Adv Drug Saf 3: 241–253. [Crossref]
5. Kashiba A, Aihis T (2018) Acquired Long-QT Syndrome: Mild but Abnormal? Intern Med 57: 773–774. [Crossref]
6. Rautaharju PM, Seybert AL, Smithburger PL, Kane-Gill SL (2009) AHA/AACFI/HRS Recommendations for The Standardization and Interpretation Of The Electrocardiogram: Part IV: The ST Segment, T and U Waves, And The QT Interval: A Scientific Statement From The American Heart Association Electrocardiography and Arrhythmias Committee, Council of Clinical Cardiology; The Merican College of Cardiology Foundation; And The Heart Rhythm Society. Endorsed By The International Society for Computerized Electrocardiology. J Am Coll Cardiol 53: 982–991. [Crossref]
7. Li M, Ramos LG (2003) Drug-Induced QT Prolongation and Torsades de Pointes. P T 68: 483–488. [Crossref]
8. Armahizer MJ, Seybert AL, Smithburger PL, Kane-Gill SL (2013) Drug-Drug Interactions Contributing To QT Prolongation in Cardiac Intensive Care Units. J Crit Care 28: 243–249. [Crossref]
9. Pickham D, Helfenbein E, Shinn JA, Chan G, Funk M, et al. (2012) High Prevalence of Corrected QT Interval Prolongation in Acutely Ill Patients Is Associated With Mortality: Results of the QT in Practice (QTIP) Study. Crit Care Med 40: 394–399. [Crossref]
10. Pickham D, Helfenbein E, Shinn JA, Chan G, Funk M, et al. (2010) How Many Patients Need QT Interval Monitoring in Critical Care Unit? Preliminary Report of The QT in Practice Study. J Electrocardiol 43: 572–576. [Crossref]
11. Fazio G, Vernuccio F, Grutta G, Re GL (2013) Drugs to Be Avoided in Patients with Long QT Syndrome: Focus on The Anaesthesiological Management. World J Cardiol 5: 87-93. [Crossref]
12. Verbeeck RK (2008) Pharmacokinetics and Dosage Adjustment in Patients with Hepatic Dysfunction. Eur J Clin Pharmacol 65: 1147-1161. [Crossref]
13. Boffito M, Jackson A, Pozniak A, Giraudon M, Kulkarni R, et al. (2015) Effect of A Modified Saquinavir/Ritonavir Dosing with Lower Dose Lead-In Phase of QTc Interval, Pharmacokinetics, Antiviral Activity and Safety in Treatment-Naive HIV-1 Infected Patients. Drugs R D 15: 141-153. [Crossref]
14. Zhang X, Jordan P, Cristea L, Salgo M, Farha R, et al. (2012) Through QT/QTc Study of Ritonavir boosted Saquinavir Following Multiple-dose administration of Therapeutic and Supratherapeutic Doses in Healthy Patients. J Clin Pharmacol 52: 520-529. [Crossref]
15. Hage FG, de Mattos AM, Khamash H, Mehta S, Warnock D, et al. (2010) QT Prolongation Is an Independent Predictor of Mortality in End-Stage Renal Disease. Clin Cardiol 33: 361-366. [Crossref]
16. Kim SM, George B, Alcivar-Franco D, Campbell CL, Charnigo R, et al. (2017) QT Prolongation Is Associated with Increased Mortality in End Stage Liver Disease. World J Cardiol 9: 347-354. [Crossref]
17. Doogue MP, Polasek TM (2011) Drug Dosing in Renal Disease. Clin Biochem Rev 32: 69-73. [Crossref]
18. Klivinyi C, Bormemans-Cimenti H (2018) Pain Medication and Long QT Syndrome. Korean J Pain 31: 3-9. [Crossref]
19. Behere SP, Shubkin CD, Weindling SN (2014) Recent Advances in The Understanding and Management of Long QT Syndrome. Curr Opin Pediatr 26: 727-733. [Crossref]
20. Briasoulis A, Agarwal V, Pturec WJ (2012) QT Prolongation and Torsades De Pointes Induced by Fluoroquinolones: Infrequent Side Effects from Commonly Used Medications. Cardiology 120: 103-110. [Crossref]
21. Yu H, Zhang L, Liu J, Liu Y, Kowey PR, et al. (2017) Acquired Long QT syndrome in Hospitalized Patients. Heart Rhythm 14: 974-978. [Crossref]
22. Tisdale JE, Wroblewski HA, Overholser BR, Kingery JR, Trujillo TN, et al. (2012) Prevalence of QT Interval Prolongation In Patients Admitted To Cardiac Care Units And Frequency Of Subsequent Administration Of QT Interval-Prolonging Drugs: A Prospective, Observational Study In A Large Urban Academic Medical Center In The US. Drug Saf 35: 459-470. [Crossref]
23. Meyer JS, Mehdadrad A, Salem BI, Kalikowski A, Kalikowski P (2003) Sudden Arrhythmia Death Syndrome: Importance of Long QT Syndrome. Am Fam Physician 68: 483-488. [Crossref]

Copyright: ©2018 Shah SK. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.