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

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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

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Table 1. Drugs with QT interval prolonging properties

Class	Drug names
Anti-arrhythmics	Sotalol, Amiodarone, Quinidine, Procainamide, Disopyramide, Flecainide, Dofetilide, Dronedarone (11)
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, Atazanavir (11), Saquinavir (14)
Anti-emetics	Ondansetron, Granisetron, Dolasetron (11)
Antihistamines	Diphenhydramine, Terbinafine, Astemizole (11)
Decongestants	Pseudoephedrine, Phenylpropanolamine (11)
Bronchodilators	Albuterol, Salmeterol, Metaproterenol, Terbutaline, Levalbuterol, Ephedrine (11)
Muscle relaxers	Tizanidine (11)
Nonsteroidal anti-inflammatory	Diclofenac, Celecoxib, Ketorolac (18)
Opiates	Methadone, Levomethadyl (11), Oxycodone, Tramadol (18)
Anti-depressants	Fluoxetine, Paroxetine, Sertraline, Citalopram, Escitalopram, Amitriptyline, Nortriptyline, Imipramine, Desipramine, Doxepin, Venlafaxine, Mirtazapine (11)
Anti-psychotics	Haloperidol, Thioridazine, Clozapine, Risperidone, Quetiapine, Chlorpromazine (11)

to boost the antiretroviral therapeutic effect [13]. A study conducted by Zhang (2012, pp 520-529) explored this association by administering a combination of SVQ-boosted RTV in therapeutic (1000/100 mg) and supratherapeutic (1500/10 mg) doses in the intervention group and moxifloxacin (400 mg) in the control group. It was reported that change in QT interval from baseline in the therapeutic dose arm was 18.9 ms at 12 hours postdose and 30.2 ms in the supratherapeutic arm at 20 hours postdose [14]. In conclusion, seropositive patients on PIs should be closely monitored for EKG abnormalities.

Additional factors predisposing patients to QT interval prolongation are renal [15] and hepatic dysfunction [16]. A study reported that high serum creatinine reflecting impaired renal function was the third strongest significant predictor of QT interval prolongation. The study included 116 participants, out of which, 40 participants with an impaired renal function exhibited prolonged QT interval ($p = 0.006$). The same study also reported that patients with hepatic dysfunction (n = 24) were significantly associated ($p = 0.006$) with QT interval prolongation [9]. A possible explanation for prolonged QT interval in patients with renal dysfunction is impaired clearance and elevated blood drug levels of drugs with proarrhythmogenic properties [17]. Similarly, hepatic dysfunction leads to impairment of drug metabolizing pathways. Cytochrome P4503A4 (CYP3A4) enzyme is most abundantly found in the liver and is utilized in over 50% of the drugs commonly used. A decline in the functionality of hepatic CYP3A4 metabolic pathway can elevate blood levels of drugs with proarrhythmogenic properties [12]. Hence, administration of drugs with known properties to prolong QT interval in patients with hepatic and renal pathologies requires meticulous EKG monitoring.

Other risk factors implicated in acquired LQTS are female sex, age > 65 years and occult genetic predisposition for LQTS [18]. Risk factor that can be modulated to prevent QT interval prolongation is electrolyte imbalance including hypokalemia, hypomagnesemia, and hypocalcemia. Cardiac conditions predisposing to LQTS are bradycardia, congestive heart failure, reduced ejection fraction and myocardial infarction [7].

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.

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