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QT Prolongation Associated with Multiple Drug-Drug Interactions

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ABSTRACT

Many drugs are known to prolong QT interval which increases the risk of development of ventricular tachycardia and cardiac arrest. The majority of sudden cardiac deaths are caused by acute ventricular arrhythmia following repolarization disturbances. An important risk factor for repolarization disturbances is the use of QT prolonging drugs. Drug interactions also play a clinically significant role in the development of QT prolongation substantially, in patients receiving multiple drugs that are prone to prolong QT interval. The present case study reports two consecutive QT prolongation events associated with drug-drug interactions in a patient during his hospital stay. A 63-years-old Asian male patient was being treated for his complaints of breathlessness, uneasiness, chest discomfort and palpitation (baseline QTc being 457 msec). During his treatment, he developed QT prolongation (QTc=494 msec) suspected to be the result of the concomitant use of levofloxacin, ondansetron, and ivabradine; QT prolongation reduced after discontinuation of the suspected drugs. In the same patient, during the later course of therapy, a concomitant use of amiodarone and fluconazole caused QT prolongation (QTc=536 msec) again. This complication is best approached with immediate discontinuation of interacting drugs and considering their alternatives. Knowledge enhancement regarding QT prolonging drug combinations and rapid ECG monitoring while using those combinations will help circumvent such adverse events.

Keyword: *QT Prolongation, Drug Interactions, Levofloxacin, Amiodarone, Fluconazole, Torsades de Pointes.*

1. INTRODUCTION

Many cardiac and non-cardiac drugs can affect cardiac repolarization and prolong the QTc interval. The use of these drugs is associated with an increased risk of serious ventricular arrhythmia [for example, Torsades de pointes (TdP)] and sudden cardiac death [1]. According to European regulatory guidelines, QTc prolongation can be distinguished into three clinically-relevant categories. For men, the cut-off points are less than 430 msec (normal), 430-450 msec (borderline) and more than 450 ms (prolonged); for women less than 450 msec (normal), 450–470 msec (borderline) and more than 470 msec (prolonged) [2,3].

Prolongation of the absolute QTc interval beyond 500 ms and/or an increase of >60 ms is regarded as indicative of an increased risk of TdP [4,5,6,7]. Many studies investigated the effects and risks of the use of a single QTc-prolonging drug [5][8][9][10]. Studies have indicated considerable risk of getting QT prolongation due to concomitant use of QT prolonging drugs which require additional ECG monitoring to establish the potential for development of QT prolongation [11].

Drug interactions play a clinically significant role in the development of QTc prolongation by various mechanisms; by reducing clearance of QT prolonging drugs (Substrates of CYP450 enzyme) by CYP450 enzyme inhibition. Drugs causing a decrease in CYP450 activity include amiodarone, diltiazem, cimetidine, azole antifungals, fluoroquinolones and erythromycin with or without additional QTc prolonging the effect. Some medicines may cause QTc prolongation by the additive effect of prolonging QT interval. For example, intravenous haloperidol to a patient receiving levofloxacin may result in an additive lengthening of the QTc interval [12]. The drug interactions can lead to QT prolongation which further can lead to the development of torsades de pointes (TdP) that can be characterized by syncope, palpitations, dizziness, seizures, and ventricular tachycardia but sometimes symptom-less when it lasts for a shorter duration of period and terminates spontaneously [12,13].

Drug interactions related adverse events can contribute to cardiac toxicity which requires monitoring of cardiac functions periodically. Cardiac related sudden deaths occur in 3-4 lacs patients yearly in the United States [13].

2. OBJECTIVE

To analyze adverse events associated with multiple drug-drug interactions involving the concomitant use of QT prolonging drugs.

3. CASE SUMMARY

A 63-years-old Asian male patient presented to the emergency room at a tertiary care hospital in Ahmedabad with chief complaints of breathlessness, uneasiness, chest discomfort and palpitation sudden in onset. Patients medical history included type 2 diabetes mellitus and hypertension since 7 years, carcinoma of larynx since 3 years and ischemic heart disease since 3 months. He was diagnosed and treated for acute left ventricular failure (LVEF 30%). The treatment included levofloxacin intravenous (IV) 500mg, cefoperazone 1.5g, ondansetron 8mg, noradrenaline, and dopamine, along with oral ivabradine 5mg, clopidogrel 75mg, and atorvastatin 20mg. On the third day of treatment, the patient developed QT prolongation (QTc = 494msec) and atrial fibrillation. QT prolongation was suspected to be an adverse effect of the combination of levofloxacin, ondansetron, and ivabradine. Upon discontinuation of the suspected trio, QT prolongation was resolved after 24 hrs (QTc = 453 msec). The atrial fibrillation was treated with amiodarone 600 mg diluted in 50 mL 5 % Dextrose solution administered at a rate of 2mL/hour up to 39 hours and then with oral amiodarone 200 mg thrice a day. On the fourth day of amiodarone therapy, the patient again developed QT prolongation (QTc = 517 msec). During later part of hospitalization, the sputum culture report revealed the heavy growth of Candida (other than Candida albicans) which was treated with intravenous fluconazole 400mg/day from the fourth day of amiodarone therapy. On the next day of fluconazole administration, there was a rise in QT prolongation (QTc = 536 msec) by 35 msec. This rise in QT prolongation was suspected to be due to the concomitant use of amiodarone with Fluconazole. It was managed by interrupting amiodarone and by switching to oral fluconazole 200 mg/day, which resulted into a decrease in the QTc prolongation (453 msec) after 24 hours.

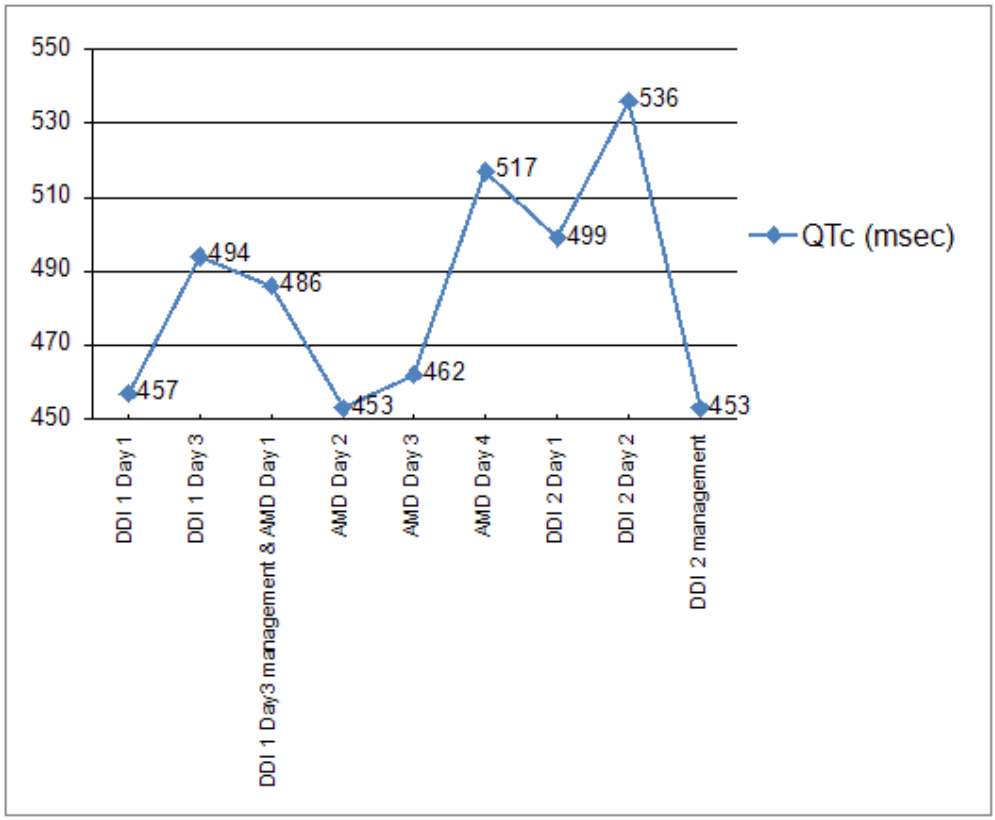

Chart 1: Effect of drug interactions on QTc interval

(DDI 1: Drug-drug interactions of Levofloxacin, Ondansetron, and Ivabradine; AMD: Amiodarone; DDI 2: Drug-drug interactions of Amiodarone and Fluconazole)(DDI 2 Day 1- 499 msec is the QTc observed in the ECG taken the early morning. Fluconazole was added to the prescription in the evening)

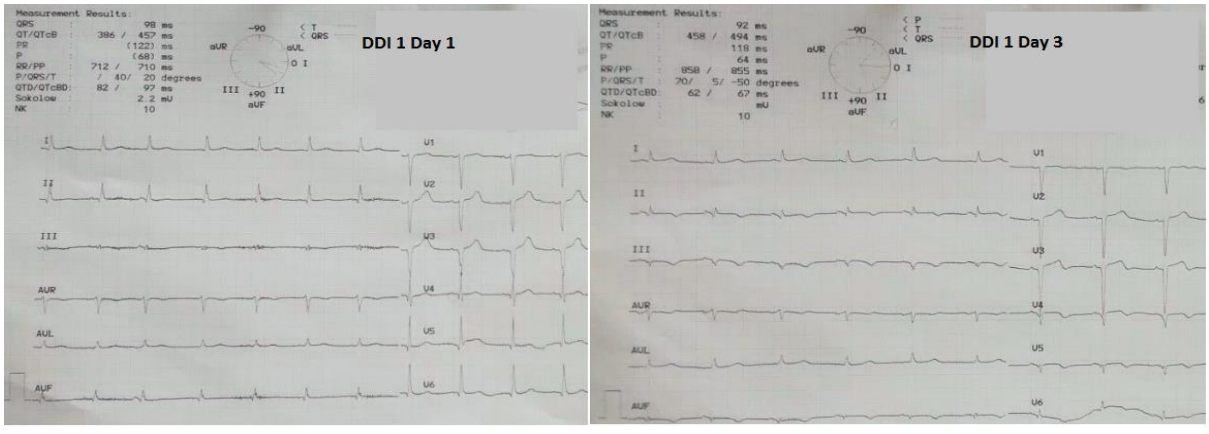

Fig. 1: Effect of drug interactions on QTc interval

3. DISCUSSION

Levofloxacin is a fluroquinolone having the potential to block the cardiac voltage-gated potassium channels and prolong QT interval [14]. Levofloxacin when combined with ivabradine and ondansetron, a 5-HT3 antagonist, the risk of QT prolongation raises. The mechanism involved in the interaction is the additive prolonging effect on QT interval [15]. In this case, on the first day of admission, levoflxacin 500 mg infusion was administered along with tablet ivabradine 5 mg/day and tablet ondansetron 8 mg/day. On the second day, levofloxacin 500 mg infusion was administered along with tablet ivabradine 10 mg/day and ondansetron 8 mg/day. On the third day, when 12-lead electrocardiogram was done, it revealed prolongation of QT interval, QTc = 494 msec. The baseline QTc was 457 msec. After an hour, ECG was repeated which confirmed prolongation of QT interval with QTc = 486 msec which appeared with atrial fibrillation.

Suspected drugs (levofloxacin, ivabradine, and ondansetron) for prolongation of QT interval were discontinued soon after the ECG investigation. On the next day to the discontinuation of suspected drugs, a 12-lead electrocardiogram was repeated that showed a fall in the QTc interval to 453 msec revealing the trio to be cardiotoxic upon concomitant use. The two days therapy with a combination of levofloxacin, ondansetron, and ivabradine caused the QTc interval prolongation by 37 msec.

To treat the Candida infection detected in sputum, intravenous fluconazole 400 mg/day was added to the prescription. Moreover, the patient was already receiving oral amiodarone 200 mg thrice daily. Fluconazole, when used concomitantly with drugs that prolong QT interval and also the substrates of CYP3A4 isoenzyme (for example, amiodarone), has the potential to increase the risk of cardiotoxicity like QT prolongation, torsades de pointes and cardiac arrest. Fluconazole has a long half-life (30 hours in adults, 46 hours in geriatrics), therefore fluconazole-mediated CYP3A4 inhibition may continue for 4 to 5 days after discontinuation of its therapy[16]. In the current scenario, QTc interval before administering fluconazole was 499 msec and it was prolonged to 536 msec after the concomitant administration of fluconazole. For the management of prolonged QTc interval, amiodarone was withheld and intravenous fluconazole was switched over to a decreased dose oral fluconazole i.e. 200mg/day. When the 12-lead electrocardiogram was repeated after 24 hours, QTc interval was reduced to 453 msec evidencing the combination to be cardiotoxic upon its concomitant use.

4. CONCLUSIONS

It was concluded that concomitant use of (i) levofloxacin, ondansetron and ivabradine and (ii) fluconazole and amiodarone was observed to prolong QT interval which may lead to life-threatening events like torsades de pointes (TdP) and sudden cardiac death if unnoticed. Hence, the use of these combinations requires close monitoring ECG to consider discontinuation or alteration in case of occurrence of QT prolongation. Additionally, health care professionals need voluntary participation in pharmacovigilance activities to promote the awareness of the drug-drug interactions and their adverse effects and to ensure safe and rational drug use in the patients.

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