Emphasis on Need to Develop Strategies to prevent Drug- Induced QTc Prolongation : Case based study following Azithromycin use

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INTRODUCTION

- Azithromycin is amongst the most commonly prescribed antibiotics worldwide. It is FDA approved for the management of a diverse range of conditions such as Acute bacterial exacerbations of Chronic Obstructive Pulmonary Disease (COPD), community-acquired pneumonia, pharyngitis/ tonsillitis and STDs.(1) This overtly used drug was prescribed nearly 28.7 million times in 2021, with nearly 86 prescriptions per 1000 people.(2)
- However, it is known to be associated with a risk of prolonged cardiac repolarization and QTc prolongation, causing an increased incidence of cardiac dysrhythmias and torsades de pointes (TdP), especially in those with other risk factors for it. (3)

OBJECTIVES

- Evaluation of the risk factors and implicated drug classes responsible for the development of QTc prolongation and subsequent arrhythmias.
- Discussion of possible strategies to prevent drug-induced QTc prolongation.

CASE PRESENTATION

- Patient is a 68-year-old female with hypertension, hyperlipidemia, anxiety, depression, diabetes and COPD on supplemental 5-liter oxygen support, with worsening shortness of breath and productive cough despite her regular inhaler use. Her symptoms were refractory to the azithromycin and steroids that she was prescribed by her pulmonologist over the phone a day prior, and thus she presented to the hospital for further evaluation.
- Her CBC, BMP and BNP levels were within normal limits. Her first EKG showed a right axis deviation with normal sinus rhythm (Figure 1) and she was continued on telemetry monitoring. Her chest x ray was consistent with emphysema without any focal infiltrates/consolidation and she tested negative for COVID-19 and influenza.
- She was started on IV ceftriaxone, steroids, and azithromycin and nebulization for managing her COPD exacerbation, due to increased oxygen requirements, sputum.
- On day 2 of hospitalization, her telemetry revealed QTc interval prolongation from 474 to 521ms with new intermittent Premature Ventricular Contractions (PVCs) (Figure 2),thus, azithromycin was discontinued. Sputum cultures grew gram negative rods and was switched to Cefdinir.
- Upon reviewing her medication list, it was found that she was also taking fluoxetine, atomoxetine, and aripiprazole, were also held subsequently.
- Monitoring of telemetry and electrolytes was continued, and subsequent decrease of the QTc interval to 485 was seen 2 days after discontinuing azithromycin.
- After returning to her baseline oxygen requirement, she was discharged on cefdinir and prednisone and told to follow up with her PCP for repeating her EKG and BMP.

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FIGURES

Figure 1: QTc:474 ms

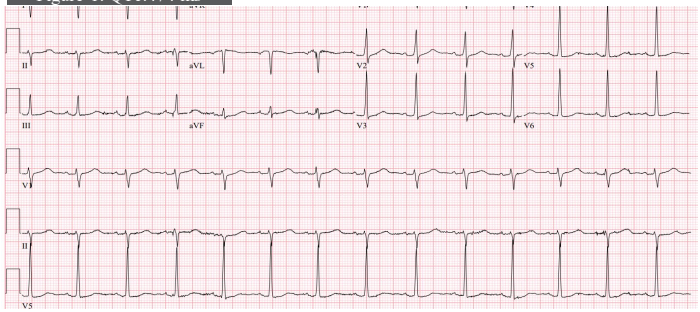

Figure 2: QTc 521ms, New PVCs

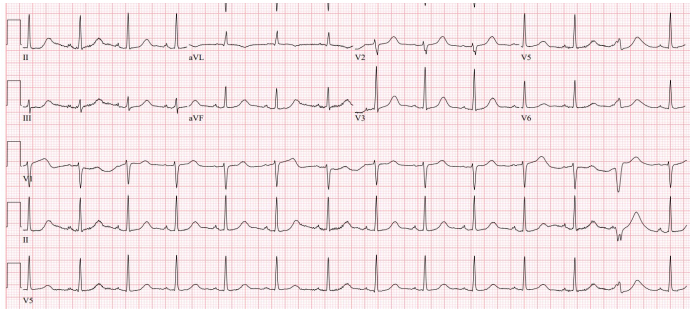

Table 1: Common Drugs causing QTc prolongation

Drug Class	Known Risk of Torsades de Pointes
Antiarrhythmics	Sotalol, Disopyramide, Flecainide, Procainamide
Antipsychotics	Haloperidol, Iloperidone, Ziprasidone, Quetiapine
Antidepressants	Escitalopram, Citalopram, Tricyclic antidepressants
Antibiotics	Flouroquinolones (Ciprofloxacin, Levofloxacin) Macrolides (Clarithromycin, Erythomycin)
Antifungals	Fluconazole, Pentamidine
Antiemetics	Domperidone, Ondansetron, Prochlorperazine
Antihistamines	Loratadine, Dimenhydrinate

DISCUSSION

- Antibiotic stewardship programs and FDA's warning related to azithromycin have caused a massive reduction in the use of Azithromycin and other antibiotics as compared to 2011. (2)
- QTc prolonging drug interactions via pharmacodynamic and pharmacokinetic mechanisms, or electrolyte abnormalities can occur with the commonly used drug classes(Table 1).(4)
- Early identification and management of potentially modifiable risk factors for drug-induced QTc prolongation such as electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia), bradycardia and recent cardioversion with a QTc prolonging drug should be routinely done.(4)
- Determining non-modifiable risk factors such as female sex, age>65 years, structural heart diseases (myocardial infarction, left ventricular hypertrophy, heart failure with reduced ejection fraction), impaired hepatic or renal function may help in tailoring the drugs used.(4)
- Pharmacists can calculate the QTc interval prolongation risk score to assess patient risk and assist in drug selection and help in any necessary dose modification in renal or liver disease patients. (5)
- Evidence-based online drug knowledge resources, such as AzCERT Drug Lists, and website prototypes like crediblemeds.org can facilitate the drug selection in outpatient clinical practice. (6)
- Baseline EKG and electrolyte levels maybe obtained prior to the use of a drug with a high risk of QTc prolongation, especially in patients with risk factors or prior episodes of QTc prolongation. The EKG may be repeated after the drug reaches a steady state or after dose modification.(4)
- Development of QTc interval prolongation risk prediction models like the Tisdale Risk score and incorporation of these models into Clinical Decision Support (CDS) tools. (4)

CONCLUSION

- We need to increase awareness and exercise caution in prescribing medications commonly implicated in QTc prolongation and know their alternatives, which is imperative to improve patient safety in both inpatient and outpatient settings.
- A thorough review of the patient's medications prior to prescribing an additional medicine in hospitals and in ambulatory settings, especially over phone encounters, can help in identifying possible drug interactions and averting fatal arrhythmias.

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