The Role of Clinical Pharmacists in Mitigating Drug-Induced QTc Prolongation: A Cross-Sectional Study

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Abstract

Background: Drug-induced QTc prolongation represents the predominant cause of acquired long QTc syndrome. Pharmacists' intervention, through the screening of at-risk patients and the provision of recommendations to prescribers for modifying drug regimens, may mitigate the adverse outcomes associated with this condition. This cross-sectional study aimed to evaluate the role of clinical pharmacists in reducing drug-induced acquired long QTc syndrome and mitigating the risk of progression toward life-threatening arrhythmias.

Methods: We included hospitalized patients who were receiving at least two concomitant QT-prolonging medications, or one QT-prolonging medication along with a diagnosis of heart failure, myocardial infarction, or sepsis in the study over three months. Using the Tisdale risk score, we provided recommendations to the prescribing physician, and acceptance rates were recorded. Additionally, the rate of QTc prolongation was assessed in the patients.

Results: The study was completed with 90 patients. The concomitant use of ondansetron and methadone was identified as the most common high-risk drug combination. A total of 56 pharmacist recommendations were made, with an estimated physician acceptance rate of 89%. Additionally, normalization of the QTc interval was observed in 14 out of 22 patients (63.6%) following pharmacists' intervention.

Conclusion: Clinical pharmacists are instrumental in the prevention of drug-induced long QTc syndrome among hospitalized patients.

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Keywords: QT Prolongation; Clinical Pharmacist; Pharmacist Intervention; Tisdale Score

Introduction

DLarge-scale population studies have defined a corrected QT interval (QTc) of 460 milliseconds or longer in women and 450 milliseconds or longer in men as an indicator of a prolonged QTc (1). A diverse range of medications have been identified as potential QTc-prolonging agents, with the incidence potentially increasing due to drug-drug interactions (2). Drug-induced QTc prolongation refers to an abnormal extension of the QTc on an electrocardiogram, which can be triggered by a variety of cardiac and non-cardiac medications. While many patients remain asymptomatic, a prolonged QTc can progress to life-threatening conditions such as polymorphic ventricular tachycardias, Torsades de Pointes (TdP), and even sudden cardiac death (3). It is essential to acknowledge that substantial QTc prolongation may occur even with the administration of standard, non-toxic therapeutic doses of the implicated drugs. However, the

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use of high-risk agents, higher drug dosages, the concomitant use of two or more QTc-prolonging agents, and drug interactions that result in increased exposure to the culprit medication collectively elevate the risk of substantial QTc prolongation and the progression toward life-threatening events. In addition to medications, electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, and less commonly hypocalcemia), myocardial ischemia or infarction, impaired hepatic and/or renal function (resulting in defective drug clearance), hypothyroidism, and pre-existing congenital defects in the QTc are among the other predisposing factors of acquired long QTc syndrome (4, 5).

Considering that numerous instances of acquired drug-induced QTc prolongation occur in hospitalized patients who are administered multiple medications or possess additional risk factors, as previously described, clinical pharmacists play a pivotal role in screening these patients and, if necessary, recommending modifications to their therapy. This study aimed to evaluate the role of clinical pharmacists in reducing drug-induced acquired long QTc syndrome and mitigating the risk of progression toward life-threatening arrhythmias.

Methods

This cross-sectional study was conducted on patients admitted to the gastroenterology/hepatology and psychosomatic wards plus the general intensive care unit (ICU) of Taleghani Hospital, a teaching hospital affiliated with Shahid Beheshti University of Medical Sciences (Tehran, Iran) from June to September 2023. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHARMACY.REC.1398.234). Patients receiving at least two concomitant QTc-prolonging medications, or one QTc-prolonging medication in conjunction with diagnoses of heart failure, acute myocardial infarction, or sepsis, met the inclusion criteria for the study. These risk factors were selected based on evidence from the Tisdale risk score for QTc prolongation (6). Necessary data collected from each patient's chart included sex, age, reason for hospital admission, medications, electrocardiographic data regarding QTc interval, presence of heart failure, acute myocardial infarction, or sepsis, and serum levels of potassium, magnesium, and calcium. Prescribed drugs classified as having a significant risk of QTc prolongation, according to the 2017 FDA guidance and the CredibleMeds QT Drugs List, were used for screening (7, 8).

Following a thorough review of the medical records, clinical pharmacists made verbal or written recommendations regarding modifications and/or adjustments in the drug regimen to the prescribing physician using the Tisdale Risk Score (5). These recommendations included reasons for intervention and suggestions to reverse or avoid the predisposing factors (e.g., alternative therapeutic options, monitoring of serum electrolyte levels, and avoiding rapid intravenous infusions of QTc-prolonging medications, etc.) if possible. The intervention cut-offs for hypokalemia, hypomagnesemia, and hypocalcemia (corrected with albumin level) were 3.5, 2, and 8.5 mg/dL, respectively.

Recommendations regarding frequent monitoring of QTc included at least three times weekly monitoring in non-ICU and multiple times a day in ICU patients in case QTc prolongation was observed. More frequent monitoring, according to the American College of Cardiology (ACC) and American Heart Association (AHA) statement, was conducted if possible (9). Consequently, the time to re-evaluate the QTc post-intervention varied on a case-by-case basis and ranged from an average of 6 to 72 hours. The corrected QT interval was calculated by the attending clinical pharmacist and a clinical pharmacy resident using the Bazett formula.

Finally, physician feedback was entered as either 'accepted' or 'rejected' in each patient's individual datasheet, and the rate of QTc prolongation reversal post-intervention was also recorded.

Results

A total of 90 patients (59 (65.5%), 24 (26.7%), and 7 (7.8%) patients from the gastroenterology, ICU, and psychosomatic wards, respectively) were included in the study. Demographic and clinical data of the patients are presented in Table 1.

Table 1. Baseline patient characteristics and clinical data

Characteristic	Value
Age – yr. (mean ± SD)	59.6 ± 16.8
Female sex – no. (%)	46 (51.1%)
Patient's ward – No. (%)	
Gastroenterology and hepatology	59 (65.5%)
wards	7 (7.8%)
Psychosomatic wards	24 (26.7%)
ICU	
Risk factors – No. (%)	
HF	12 (13.3%)
MI	3 (3.3%)
Sepsis	2 (2.2%)
Electrolyte levels – mg/dL (mean ± SD)	
K	3.8 ± 0.5
Mg	2.1 ± 0.7
Ca	9 ± 0.7
Patients on diuretics – No. (%)	23 (25.6%)

Yr: years old, SD: standard deviation, ICU: intensive care unit, HF: heart failure, MI: myocardial infarction, mg/dL: milligrams per deciliter, K: potassium, Mg: magnesium, Ca: calcium

The most common QT-prolonging combinations are shown in Table 2, with the concomitant use of methadone and ondansetron (8.9%) being the most prevalent combination.

Table 2. Most commonly identified QTc-Prolonging combinations

Combination	Frequency – No. (%)
Methadone + Ondansetron	8 (8.9%)
Ciprofloxacin + Metronidazole	6 (6.7%)
Methadone + Haloperidol	4 (4.4%)
Methadone + Ciprofloxacin + Azithromycin	3 (3.3%)
Ciprofloxacin + Ondansetron	3 (3.3%)
Methadone + Citalopram	3 (3.3%)

No: number

In 56 out of 90 included patients (62.2%), at least one verbal or written recommendation regarding modifications in the drug regimen was made by the clinical pharmacist. These modifications included offering safer pharmacologic alternatives, providing administration notes, correcting and monitoring serum electrolyte levels, and frequently monitoring the QTc interval by obtaining ECGs if needed. Additionally, they involved educating nursing staff on drug administration, including the maximum intravenous administration rate and concentration. In 50 out of 56 cases (89%), recommendations were implemented at the discretion of the prescribing physician, resulting in modifications to the therapeutic regimen. In the remaining six cases (11%), the pharmacist's recommendations were not implemented. QTc prolongation was observed in 22 patients after initiation of medications. In 14 out of mentioned 22 patients, the QT interval normalized following the implementation of pharmacist's recommendations and the elimination of reversible patient risk factors. Therefore, the "after" value recorded for QTc interval was shorter in 63.6% of cases in whom clinical pharmacist's recommendation was utilized. Table 3 represents the abbreviated distribution of clinical pharmacists' recommendations and their acceptance.

Table 3. Distribution of clinical pharmacists' recommendations and their acceptance.

Pharmacist Recommendation Status	Frequency – No. (%)
At least one recommendation	56 (62.2%)
• Recommendation(s) implemented	50 (55.6%)
• Recommendation(s) not implemented	6 (6.7%)
No recommendations	34 (37.8%)
Total	90 (100%)

No: number

Discussion

Clinical pharmacists can assume ever-expanding roles, such as optimizing patients' pharmacotherapy to significantly improve patient care. The nature of interactions between clinical pharmacists and physicians influences their teamwork and enhances the quality of patient care (10). Ullah Humzah et al. recommend pharmacists improve their knowledge and awareness of QTc prolongation when conducting drug regimen assessments (11). There are limited studies evaluating the impact of clinical pharmacists' interventions on alleviating drug-induced QTc prolongation. In a French study, the impact of pharmacists' interventions has been evaluated on the combination of citalopram or escitalopram with other medications that induce QTc prolongation (11). It was revealed that most of the prescriptions related to potential drug-drug interactions of citalopram or escitalopram (62.5%) changed in response to pharmacists' intervention when initiated during the hospital stay. Antiarrhythmic agents, antipsychotics, and antiemetics (52%, 32%, and 8% respectively) were the most common medication classes involved in QT-prolonging drug-drug interactions with citalopram and escitalopram. Similar to this study, 89% of our clinical pharmacists' recommendations were accepted by prescribing physicians, leading to a significantly shorter "after" value recorded for QTc interval in 63.6% of cases where the recommendations were utilized. However, in contrast to the mentioned study above, our study also involved other medications with possible QTc-prolonging effects. In a parallel-group study on 149 ICU patients conducted by Ng et al., the occurrence of drug-induced QTc prolongation was frequently lower in the pharmacists' intervention group versus the standard group (19% Vs. 39% respectively; p=0.006) . The pharmacist implemented a standardized algorithm, including routine monitoring of ECG, assessment of hepatic and renal function, evaluation of serum electrolytes, and screening for the highest-risk QTc-prolonging medications to make recommendations to the medical team. The prescriber acceptance rate of pharmacist recommendations was reported to be 70% (12).

Based on our results, we recommend the routine evaluation of prescription charts for patients with drug-induced long QTc syndrome by a clinical pharmacist. This evaluation should include modifications to drug regimens to reduce the incidence of significant drug-induced QTc prolongation and the risk of life-threatening complications. The sample size of observed patients in our study was small. Future studies with a larger patient population may provide a more accurate estimation of the impact of clinical pharmacists' interventions in this area.

Conflicts of Interest

The authors reported no conflicts of interest.

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