ORIGINAL ARTICLE

Assessment of Drug Induced QT Interval Prolongation at a tertiary care, Baptist Hospital, Bangalore

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ABSTRACT

Aim: To investigate the drug induced QT-interval prolongation in hospital inpatients, predictors of risk factor for QT-interval prolongation and drug-drug interactions.

Methodology: It is a prospective observational study conducted in inpatient setting. The data collected in pre design data collection form for 110 patients, who are assessed for the period of six months. The prescription with at least one QT-interval prolonging drugs were considered for this study. The collected data included demographics, mean change in QT-interval with drugs, ECG data and safety analysis data.

Result: The total number of patients screened was 110. Among the study patients most of them 50.91% were older age. Major co-morbidities were diabetes mellitus 39(35.45%) and hypertension 36(32.72%). There was a high prevalence (46.45%) of QT-interval prolongation. The mean QTc in prolonged group was 495±34.4ms. Ondansetron (61.18%), Metronidazole (58.18%), Ciprofloxacin (20.9%), Azithromycin (16.36%) and Domperidone (11.81%) were associated with marked QTc-interval prolongation. Female sex, longer hospitalization, electrolyte abnormalities and older age were associated with drug induced QT-interval prolongation. 97(88.18%) prescriptions showed drug interaction involving QT-interval prolongation. The most common drug interaction was found to be between ondansetron and metronidazole in 41 prescription followed by ondansetron and ciprofloxacin in 15 prescriptions. Of the 97 interventions proposed, the most frequent suggestion was on stop/avoid/dose adjustment (13.40%) followed by ECG monitoring (10.40%). 16.49% of interventions were accepted

Conclusion: This study demonstrates the high prevalence of a prolonged QT-interval in patients. Cardiac drugs and antibiotics were frequently involved in drug induced QT-interval prolongation. A simple ECG and a calculated QT interval can be used to plan management and caution consultant on probable electrolyte abnormalities and drug therapies. The current study demonstrated the importance of routine medication review and the need of a pharmacist in a multidisciplinary team.

Key words: QT-interval prolongation, ECG data, prescription pattern

INTRODUCTION

QT interval prolongation can lead to the ventricular arrhythmia known as torsade de pointes (TdP), which can result in sudden cardiac death. In recent years, the potential for QT interval prolongation and TdP has received increased attention, partly owing to increased recognition of the risks and catastrophic nature of this disease[2,9-10].

Typical features of TdP include an antecedent prolonged QT interval, particularly in the last sinus beat preceding the onset of the arrhythmia, a ventricular rate of 160 to 250 beats per minute, irregular RR intervals, and a cycling of the QRS axis through 180 degrees every five to 20 beats. TdP is usually short-lived and terminates spontaneously. However, most patients experience multiple episodes of the arrhythmia, and episodes can recur in rapid succession, potentially degenerating to ventricular fibrillation and SCD[7].

The QT interval is measured on the electrocardiogram (ECG) and represents the ventricular depolarization and repolarization[1]. The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave. This electrical activity of the heart is mediated through channels, complex molecular structures within the myocardial cell membrane that regulate the flow of ions in and out of cardiac cells. The rapid inflow of positively charged ions (sodium and calcium) results in normal myocardial depolarization. When this inflow is exceeded by outflow of potassium ions, myocardial repolarization occurs. Malfunction of ion channels leads to an intracellular excess of positively charged ions by way of an inadequate outflow of potassium ions or excess inflow of sodium ions. This intracellular excess of positively charged ions extends ventricular repolarization and results in QT interval prolongation[6].

Over the last two decades, intense research has improved our knowledge of the mechanisms and risks of drug-induced QT prolongation. Most of this research has been conducted by the pharmaceutical industry and has arisen following market withdrawals of medicines that caused torsades de pointes arrhythmia, such as cisapride and some non-sedating antihistamines[3].

The QT interval is influenced by heart rate. The RR interval preceding the QT interval should be measured for rate correction. Several formulae may be used to correct the QT interval for the biophysical effect of heart rate (QTc), but none is perfect. The most commonly used formulae are Fridericia's cube root formula (QTc = QT/RR1/3) and Bazett's square root formula (QTc = QT/RR1/2). Of the two, Bazett's formula is the more popular, but Fridericia's correction is preferred because it is more accurate at the extremes of physiological heart rate[1].

The main objective of the study was to aimed to investigate the drug induced QT-interval prolongation in hospital inpatients, predictors of risk factor for QT-interval prolongation and drug-drug interactions.

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MATERIALS AND METHODS

QT prolongation is a measure of delayed ventricular repolarisation. Excessive QT prolongation can predispose the myocardium to the development of early after-depolarisations, which in turn can trigger re-entrant tachycardia's such as TdP. Although the relationship between QT interval duration and the risk of TdP is not fully understood, a corrected QT interval (QTC) of >500ms1 or an increase in the QTC of >60ms2 is generally considered to confer a high risk of TdP in an individual patient.The QT interval varies with heart rate. A number of formulas are used to correct the QT interval for heart rate. Once corrected it is expressed as the QTc interval. The QTc interval is reported on the ECG printout.

This study was conducted on 110 patients in all wards at Bangalore Baptist Hospital (BBH), Bangalore Baptist Hospital is a 300 bedded hospital providing secondary health care to people.The patient demographics and all medically relevant information was noted in a predefined data collection form. Alternatively, these case charts were reviewed for QT-interval prolongation due to drugs, unaccepted abbreviations, capture of relevant information in case sheet, electrolyte abnormalities, drug interactions and pharmacist's intervention. The changes and the daily notes in the case sheets were followed until the patient was discharged or shifted to other wards. The ECG interpretation, Micromedex, Medscape and references books were used as tools to review the prescription and case charts. The clinical pharmacist's intervention was done by suggesting physician about the drug related problems. The data were stored confidentially and subjected to further analyst.

RESULT AND DISCUSION

The data of 110 patients admitted to inpatients ward during the period October 2015 and March 2016 were analysed for drug induced QT-interval prolongation. The mean age of study population was 54.14 (±17.56).Among the study population 56(50.91%) were geriatric patients and 4(3.63%) were renal impairment patients. Major co-morbidities were diabetes mellitus 39(35.45%) and hypertension 36(32.72%). It remains unclear whether such relative gender differences in adults reflect an intrinsically greater tendency in women to develop torsade de pointes or whether men have some protective factor(s).Majority of the study subjects were in group of geriatric (50.91%) which may have influenced the prolongation of QT-interval as more of the older people have structural heart problem.

Out of 110 study population, 76.36% were taking two QT interval prolonging drugs, which is in contrast to study conducted in Switzerland[30]. About 6.36% of study population were taking 3-5 medication, which consists of total of 14 QT interval prolonging drugs. About 35.45% of study population were taking more than 10 drugs, which consists of 80 QT interval prolonging drugs. About 58.18% of study population were taking 6-10 medication, which consists of 127 QT interval prolonging drugs. This results shows that as the number of medication dispensed increases the chance of QT interval prolonging drugs also increases. Most common primary diagnosis was gastrointestinal 44 followed by cardiac 21 and other. Most of the QT prolongation were also seen in to gastrointestinal and cardiac patients (Table 1).

Among 110 study population, 45.45% had prolonged QTc-interval, 26.36% had age more than 68 years old, 57.27% had female sex, 3.63% had bradycardia, 15.45% had hypokalemia, 88.18% had more than two QT interval prolonging medication. About 9.09% study population had arrhythmias and 8.18% of patients were already using calcium channel blockers. Out of 110 study population, 76.36% were taking two QT interval prolonging drugs. The frequency of QT interval prolonging drugs (Table 2).

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Among 110 study population, 1.8% of patients who took Ivabradine had a QTc-interval increase of 28.59 Ondansetron (61.18%), Metronidazole (58.18%), Ciprofloxacin (20.9%), Azithromycin (16.36%) and Domperidone (11.81%) were associated with marked QTc-interval prolongation.

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Out of 110 inpatients record analyzed during the study period, of which 97(88.18%) prescriptions showed drug interaction involving QT-interval prolongation. The study prescription comprised of 120 major interactions and 2 contraindicated interactions. Among 110 prescriptions, 113(92.62%) were pharmacodynamics interaction followed by 9(7.38%) were pharmacokinetic interactions. The summary of drug-drug interaction resulting in QT-interval prolongation is presented in Table 5.

Out of the 97 interventions proposed, the most frequent suggestion was on stop/avoid/dose adjustment (13.40%) followed by ECG monitoring (10.40%). 16.49% of interventions were accepted and therapy was changed. The most common drug interaction was found to be between ondansetron and metronidazole in 41 prescription followed by ondansetron and ciprofloxacin in 15 prescriptions. The details of drug interaction involving QT-interval prolongation is listed in Table 6.Most of the interaction 113(92.62%) were synergistic in nature followed by 9(7.38%) metabolism in nature. The mechanism of QT-interval prolonging drug interaction in given in Table 6.

The drug interaction software by Micromedex-2 showed that monitoring for the adverse drug effects 105(86.06%) was the most popular intervention followed by time spacing 13(10.05%) following QT-interval prolonging drug interactions. The management of QT-interval prolonging drug interaction is shown in Table 7

Table 1: Primary diagnosis and QTc interval

Diagnosis	n	Prolo ged QT	Mean QT(SD)
Cardiac	21	13	479.84(14.10)
Neurological	7	2	486(14.14)
Respiratory	12	6	470(34.13)
Infection	10	6	490(18.49)
Cancer	11	3	467(12.22)
Gastrointestinal	44	18	495(25.14)
Miscellaneous	15	2	478(10.12)

Table 2: Number of QT interval prolonging drugs

Number of QT interval prolonging drugs	Male	Female	Total
1	5(4.54%)	8(7.27%)	13(11.81%)
2	37(33.63%)	47(42.72%)	84(76.36%)
3	7(6.36%)	5(4.54%)	12(10.9%)
4	0	1(0.9%)	1(0.9%)

Table 3: Relationship between poly pharmacy and number of QT interval prolonging drugs

Number of Drug Dispensed	n	Number of QT interval prolonging drugs
3-5	7(6.36%)	14(6.33%)
6-10	64(58.18%)	127(57.46%)
>10	39(35.45%)	80(36.19%)

Table 4 Factors associated with increased risk of QT interval prolongation

Parameters	n%
Severity	
Contraindicated	2(1.64%)
Major	120(98.36%)
Pharmacodynamics Interaction	113(92.62%)
Management	
Monitoring	105(86.06%)
Dose adjustment	4(3.27%)
Time spacing	13(10.65%)

Table 5 Summary of QT interval prolonging drug interaction

Risk factor	n%
Prolonged QTc	50(45.45%)
Age > 68 year	29(26.36%)
Female sex	63(57.27%)
Bradycardia	4(3.63%)
Hypokalemia	17(15.45%)
Hypomagnesaemia	1(0.9%)
Heart Failure(low EF)	6(5.45%)
≥2 QTc prolonging drugs	97(88.18%)
Arrhythmias	10(9.09%)
Calcium channel blockers	9(8.18%)

Table 6: Details of QT interval prolonging drug interactions

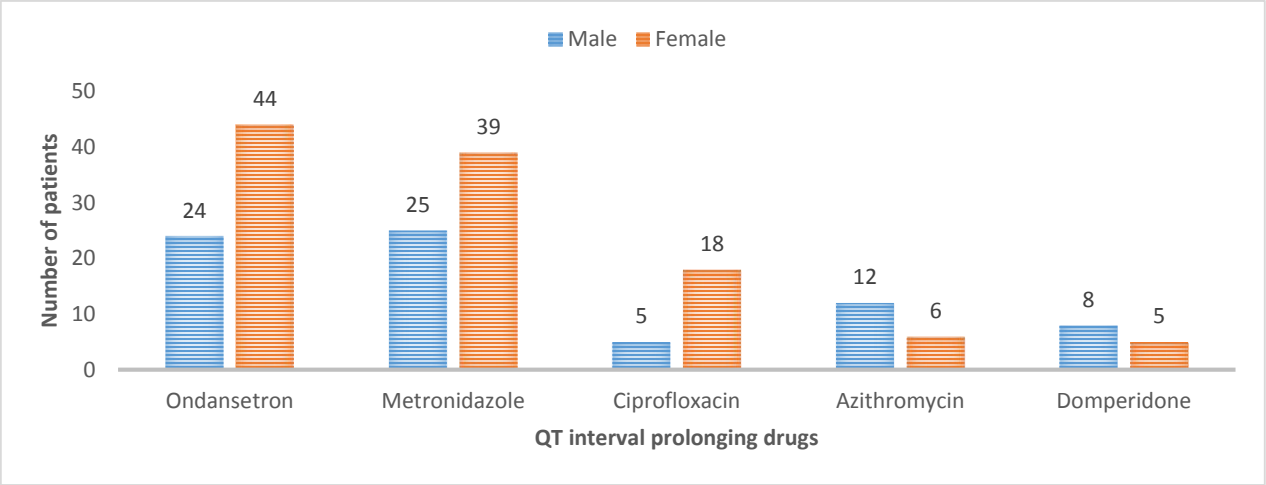
Precipitant drug	Mechanism	Frequency	Management
Ondansetron			
Metronidazole	Additive effect on QT-interval	41	Monitor ECG
Ciprofloxacin	Additive effect	15	Monitor ECG
Clarithromycin	Reduced metabolism	1	Adjust dose
Promethazine	Additive effect	5	Monitor ECG
Atorvastatin			
Domperidone	Inhibition of CYP3A4	3	Adjust dose
Azithromycin			
Metronidazole	Additive effect	4	Monitor ECG
Domperidone	Additive effect	3	Monitor ECG
Fluconazole	Additive effect	4	Monitor ECG
Ondansetron	Additive effect	6	Monitor ECG
Ciprofloxacin			
Haloperidol	Additive effect	1	Monitor ECG
Metronidazole	Additive effect	13	Time spacing
Promethazine	Additive effect	1	Monitor ECG
Domperidone			
Metronidazole	Additive effect	4	Monitor ECG
Cilnidipine	Inhibition of CYP450	2	Monitor ECG
Amlodipine	Inhibition of CYP3A4	1	Monitor ECG
Levofloxacin	Additive effect	1	Monitor ECG
Fluconazole			
Metronidazole	Additive effect	3	Monitor ECG
Domperidone	Inhibition of CYP3A4	2	Monitor ECG
Ivabradine			
Venlafaxine	Additive effect	2	Monitor ECG
Metronidazole			
Amiodarone	Additive effect	2	Monitor ECG
Levofloxacin	Additive effect	1	Monitor ECG
Promethazine	Additive effect	7	Monitor ECG

Table 7: Management of QT interval prolonging drug interaction

Management of pDDI	Male	Female	Total
Continue with monitoring	36(29.50%)	69(56.55%)	105(86.06%)
Dose adjustment	3(2.45%)	1(0.8%)	4(3.27%)
Time spacing	3(2.45%)	10(8.19%)	13(10.65%)

Top five drugs associated with marked QTc-interval prolongation is represented in figure 1.

Fig. 1 Top five drugs associated with QT interval prolongation



CONCLUSION

This study attempted to assess the prescriptions containing QT-interval prolonging drugs in hospital inpatient setting. This study demonstrates the high prevalence (46%) of a prolonged QT-interval in patients. It was noted that 88.18% had more than two QT interval prolonging medication during the hospital stay. Extensive polypharmacy was observed with increase in QT-interval prolonging medication as the total number of drug increased.

This study identified several drugs that had a pronounced effect on the QT-interval. Many of them, such as several antibiotics, and amiodarone have long been known to affect QT duration. The study revealed older age, female sex, bradycardia, hypokalemia as the strong predictors of QT-interval prolongation. A simple ECG and a calculated QT interval can be used to plan management and caution us on probable electrolyte abnormalities and drug therapies.Out of 110 prescriptions, 97(88.18%) prescriptions showed drug interaction involving QT-interval prolongation. These data can be used to educate clinicians on safe medication use. Computerized clinical decision support could be applied to aid in the detection of these events. The use of the drug interaction checker software has greatly aided the study by assessing the findings mentioned above more easily; this would have been harder to achieve if done manually. This study concluded that the pharmacists can play significant role in assessing and controlling drug interaction.

The study reported that about 28% of intervention proposed were accepted by physician. The current study demonstrated the importance of routine medication review and the need of a pharmacist in a multidisciplinary team.

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