A PROSPECTIVE STUDY ON ASSESSMENT OF DRUG INDUCED QT INTERVAL PROLONGATION IN INPATIENT DEPARTMENT AT A TERTIARY CARE HOSPITAL

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INTRODUCTION

The QT interval is measured on the electrocardiogram (ECG) and represents the ventricular depolarization and repolarization (Niemeyer MN et al, 2015). 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 out flow 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 in flow of sodium ions. This intracellular excess of positively charged ions extends ventricular repolarization and results in QT interval prolongation (Viskin S 1999).

The long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram (ECG) (Moss AJ 2003). This syndrome is associated with an increased risk of a characteristic life-threatening cardiac arrhythmia, known as torsade de pointes (TdP). The primary symptoms in patients with LQTS include palpitations, syncope, seizures, and sudden cardiac death (El-Sherif N and Turitto G 2003). Generally, QT prolongation is considered when the QTc interval is greater than 440 ms (men) and 460 ms (women), although arrhythmias are most often associated with values of 500 ms or more. Interval varies from drug to drug and from patient to patient. Unfortunately, the extent of QT prolongation and risk of TdP with a given drug may not be linearly related to the dose or plasma concentration of the drug because patient and metabolic factors are also important (for example, sex, electrolyte concentrations, etc.). Furthermore, there is not a simple relation between the degree of drug induced QT prolongation and the likelihood of the development of TdP, which can occasionally occur without any
substantial prolongation of the QT interval (Yap YG and Camm AJ 2003).

Table 1 QTc values for normal and prolonged QT interval after correction with Bazett’s formula

| Characteristics          | QTc values by age group and sex (ms) |
|--------------------------|-------------------------------------|
|                          | 1-15 years | Adult males | Adult females |
| Normal                   | <440       | >430        | >450          |
| Borderline               | 440-460    | 430-450     | 450-470       |
| Prolonged (top 1%)       | >460       | >450        | >470          |

At what degree of prolongation of correct QT (QTc) interval torsade de pointes is likely to develop is uncertain. However a QTc interval exceeding 500 milliseconds is generally considered of particular concern, but this is not an exact figure. In addition, there is uncertainty about what constitutes an important change in QTc interval from baseline, although, in general, increases of 30 to 60 milliseconds should raise concern, and increases of over 60 milliseconds raise clear concerns about the potential for arrhythmias. Because of these uncertainties, historically, many drug manufacturers and regulatory agencies contraindicated the concurrent use of drugs known to prolong the QT interval, and a ‘blanket’ warning was often issued because the QT prolonging effects of the drugs are expected to be additive. However, regulatory guidance developed in 2005 (European Medicines Agency 2005), provides recommendations for the assessment of risk of a non-antiarrhythmic drug, and in particular outlines the criteria for studying these effects, in what is called a ‘Thorough QT/QTc study’ which is considered the definitive study design. One of the key criteria of such studies is that it should include use of a positive control, i.e. a drug known to cause an increase in QTc interval of about 5 milliseconds [moxifloxacin is often used for this purpose].

**METHODOLOGY**

Study was conducted in all wards at Bangalore Baptist Hospital (BBH), Bangalore. Bangalore Baptist Hospital is a 300 bedded hospital providing secondary health care to people. Study was conducted for a period of 6 months.

Inclusion Criteria: All patients who were taking at least one QT Interval Prolongation medication and had a hospital stay of at least 48 hours. Exclusion Criteria: Patients admitted to Pediatric and Obstetric and pregnancy ward.

The patient demographics and all medically relevant information was noted in a predefined data collection form. Alternatively, these case charts were reviewed for Assessment of Drug induced QT interval prolongation

Unacceptable abbreviations, capture of relevant information in case sheet, electrolyte abnormalities, drug interactions and pharmacists 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 analysis using appropriate software.

**RESULT AND DISCUSSION**

The study population had hospital stay length of less than five days which is in contrast to study conducted in Tamil Nadu (George TK et al, 2015). However the author had looked at only medical ICU which may have increased the length of hospital stay. Out of 110 study population, 76.36% were taking too Many drugs have been implicated in QT prolongation, but the actual risk of this occurring is unclear in most cases. When prescribing drugs that prolong the QT interval, the balance of benefit versus harm should always be considered (Isbister GK 2015). The goal of this study was to investigate drug induced QT-interval prolongation in a hospital inpatients.

**Patient’s demographic data**

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) which is in agreement with the results of study revealed female preponderance which is similar to study conducted by Tisdale JE et al (2014). Another study conducted in medical ICU reported an equal gender distribution, consisting of 49% females the patients were also quite morbid (George TK et al, 2015). It might be because women are more susceptible to the development of QT-interval prolongation induced torsade de pointes (Lehmann MH et al, 2009). 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.

**Table 2 Patient Demographic details**

| Parameter                  | Male | Female |
|----------------------------|------|--------|
| Patient age (Years)        | n    | %      |
| 20-30                      | 4    | 0.36   |
| 31-40                      | 2    | 1.81   |
| 41-50                      | 13   | 11.81  |
| 51-60                      | 2    | 1.81   |
| 61-70                      | 12   | 10.90  |
| 71-80                      | 12   | 10.90  |
| 81-90                      | 2    | 1.81   |
| Sub total                  | 47   | 42.27  |
| Special population         |      |        |
| Geriatric                  | 27   | 24.59  |
| Renal impairment           | 1    | 0.9    |
| Co-morbidities             | 28   | 25.45  |
| Diabetes Mellitus          | 19   | 17.27  |
| HTN                        | 17   | 15.45  |
| CKD                        | 1    | 0.9    |
| Pulmonary Disorder         | 5    | 4.54   |
| CNS Disorder               | 5    | 4.54   |
| Hypothyroidism             | 4    | 3.63   |
| Total                      |      |        |

| Percentage |          |
|------------|----------|
| Male       | 57.27    |
| Female     | 42.73    |

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It was observed that 83.39 (35.45%) had diabetes mellitus type 2 and 36 (32.72%) hypertension as a major comorbidities, which is similar to study conducted in Tamil Nadu (George TK et al., 2015). Comorbidity increases the total burden of the illness in a patient and also contributes to clinical outcomes as well as to economic outcomes. Major primary diagnosis were cardiac and gastrointestinal in nature and these were also associated with prolonged QT-interval. A prospective observational study conducted in US showed that major primary diagnosis as cardiac in nature (Tisdale JE 2012).

Most of QT interval prolonging drugs, which is in contrast to study conducted in Switzerland. 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 more than 10 drugs, which consists of 10 drugs, which consists of

### Table 3 Primary diagnosis and QTc interval

| Diagnosis       | Total number | Prolonged QT | Mean QT(SD) |
|-----------------|--------------|--------------|-------------|
| Cardiac         | 21           | 13           | 479.84±14(14) |
| Neurological    | 7            | 2            | 486.14±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)   |
| Total           | 120          | 50           | 480.83(10.24) |

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.

In my study, almost 46% of the population had a prolonged QT interval. Other studies have also shown similar trends in the prevalence of a prolonged QT. In a study by Pickham et al 2012 it was 24%, Kozik et al 2012 it was 52% and Tisdale et al, 2012 28%.

### Table 4 Demographic and clinical variable differences between those with normal and prolonged QTc

| Predictors(n) | QT normal-n(% or) | QT prolonged-n(% or) |
|---------------|-------------------|---------------------|
| Age(110)      | Mean±SD(n) Total=60 | Mean±SD(n) Total=50 |
| Male(47)      | 50.58(50)          | 23.48(51.03)        |
| Female(53)    | 37.58(50)          | 24(61.27)           |
| Reason for admission | 10 | 2 |
| Respiratory   | 17                | 35                  |
| Hemodynamic   | Neurologic        | 3                   |
| Clinical History | Diabetes(20) | 10(50) | 10(50) |
| Hypertension(22) | 8(36.36) | 14(63.64) |
| Old CVA(8)    | 4(50)             | 4(50)               |
| Renal failure(2) | 1(50) | 1(50) |
| Lab parameters | Sodium(105) | 135.7±18.56(55) | 136.6±15.35(50) |
| Potassium(90) | 3.8±1.24(44)      | 3.6±1.46(46)       |
| Calcium(50)   | 4.5±1.4(20)       | 4.3±1.23(30)       |
| Magnesium(67) | 2.3±1.4(30)       | 2.1±1.37(37)       |
| Creatinin(40) | 1.03±1.3(15)      | 1.4±1.25(35)       |
| Glucose(70)   | 146.3±148(40)     | 148.9(40)          |
| Arthritisias(10) | 2 | 8 |
| HR on ECG(10) | 10(23.37)         | 100(28.50)         |
| QTc | 405.7±11.9 | 495±34.8 |

**Drug associated with QT-interval prolongation**

The average number of drugs per prescription is an important index of a prescription audit. It is preferable to keep the number of drugs per prescription as low as possible to minimize the risk of drug interactions and hospital costs. The mean number of drugs received by patients in the present study (10.03) was higher compared to report from another study which recorded a mean of 7.8 drugs (Curts LH et al., 2003). This may be related to the physician’s tendency to polypharmacy and also multi-diagnosed prescriptions written for some patients. Polypharmacy is defined as concomitant use of five or more drugs and it could enhance drug interactions and drug related problems (Vitikil KK et al., 2006). Extensive polypharmacy (94.45%) that is more than five drugs were prescribed in all the patients. Polypharmacy in some instance becomes necessary especially when the patient has some co-morbid conditions. Since the vast majority of patients in our study experienced a QT-interval prolongation and the prevalence of inherited long QT syndrome is low, it is very likely that the cause for the observed QTc-interval prolongation was acquired. Given the clear evidence that several drugs were associated with a statistically significant QTc-prolongation in our study, drug-induced QT-prolongation appears to be a major contributor to the observed QTc-prolongation. Because individual drugs mostly showed a median QTc-prolonging effect of <10ms and the average observed QT prolongation was 18.78 ms.

This study identified several drugs that had a pronounced effect on the QTc-interval. Many of them, such as several antibiotics, and amiodarone have long been known to affect QT duration. Among 110 study population, 1.8% of patients who took Ivaladrine had a QTc-interval increase of 28.59ms. Ondansetron (61.18%), Metronidazole (58.18%), Ciprofloxacin (20.9%), Azithromycin (16.36%) and Domperidone (11.81%) were associated with marked QTc-interval prolongation. However another study reported azithromycin, ondansetron, levofloxacin, amiodarone, haloperidol, and fluconazole as the potential QT prolonging drugs used (George TK et al., 2015). In contrast to this study, another study by Keller GA et al reported clarithromycin, haloperidol, tramadol, amiodarone, glyceryl trinitrate, amoxicillin + clavulanic acid, amoxicillin + sulbactam, ampicillin + sulbactam, fentanyl, Piperacillin + tazobactam, and diazepam as the major drugs associated with prolonged QT-interval prolongation. This difference in the result might be due to the difference the study design as this current study was single centre and the comparator was multicentre study (Keller GA et al., 2015).

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. Among 9.09% study population had arrhythmias and 8.18% of patients were already using calcium channel blockers. Similarly, another study conducted in medical inpatient reported hypokalemia, female sex, using more than 2 QT-interval prolonging drugs and liver disease as possible risk factor for drug induced QT-interval prolongation (Pasquier M et al., 2012). Another study of corrected QT interval prolongation in acutely ill patients showed female sex, QT-prolonging drugs, hypokalemia, hypocalcaemia, hyperglycemia, high creatinine, history of stroke, and hypothyroidism as a
CONCLUSION

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.

Reference

1. Niemeijer MN, Berg ME, Eijgelsheim M, Rijnbeek PR, Stricker BH. Pharmacogenetics of Drug-Induced QT Interval Prolongation: An Update. Drug Saf. 2015; 38:855-857.
2. Viskin S. Long QT syndromes and torsade de pointes. Lancet. 1999; 354:1625-1633.
3. Moss AJ. Long QT Syndrome. JAMA. 2003; 289:2041.
4. El-Sherif N, Turitto G. Torsade de pointes. Curr Opin Cardiol. 2003; 18:6.
5. Yap YG, Camm AJ. Drug Induced QT prolongation and Torsades de pointes. Heart. 2003; 89:1363-1372.
6. European Medicines Agency. Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. November 2005. Available at: http://www.ema.europa.eu/2009.pdf (accessed 12/12/2015)
7. George TK, Chase D, Peter JV, Satyendra S, Kavitha R, George LR et al. Association between a prolonged corrected QT interval and outcomes in patients in a medical Intensive Care Unit. Indian J Crit Care Med. 2015;19:326-32.
8. Isibst GK. Risk assessment of drug-induced QT prolongation. Aust Prescr. 2015; 38:20-4.
9. Vändel E, Marynissen T, Reyntens J, Spriet I, Vandenberge J, Willems R et al. Frequency of use of QT-interval prolonging drugs in psychiatry in Belgium. Int J Clin Pharm. 2014; 36(4):757-65.
10. Tisdale JE, Jaynes HA, Kingery JR, Overholser BR, Mourad NA, Trujillo TN et al. Effectiveness of a Clinical Decision Support System for Reducing the Risk of QT Interval Prolongation in Hospitalized Patients. Circ Cardiovasc Qual Outcomes. 2014; 7(3): 381-390.
11. Lehmann MH, Timothy KW, Frankovich D, Fromm BS, Keating M, Locati EH et al. Age-Gender Influence on the Rate-Corrected QT Interval and the QT-Heart Rate Relation in Families With Genotypically Characterized Long QT Syndrome. JACC. 2009; 29(1):93-9.
12. Tisdale JE, Wroblewski HA, Overholser BR, Kingery JR, Trujillo TN, Kovacs RJ. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QTinterval-prolonging drugs: A prospective, observational study in a large urban academic medical center in the US. Drug Saf. 2012; 35:459-70.
13. Pickham D, Helfenbein E, Shinn JA, Chan G, Funk M, Weinacker A, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: Results of the QT in Practice (QTIP) Study. Crit Care Med 2012; 40:394-9.
14. Kozik TM, Wung SF. Acquired long QT syndrome: Frequency, onset, and risk factors in intensive care patients. Crit Care Nurse 2012; 32:32-41.
15. Curtis LH, Ostbye T, Sendersky V, Hutchinson S, LaPointe NM, Al-khatib SM et al. Prescription of QT-Prolonging Drugs in a Cohort of About 5 Million Outpatients. Am J Med. 2003; 114:135-141.
16. Viktil KK, Blix HS, Moger TA, Reivkam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol. 2006; 63(2): 187-195.
17. Keller GA, Alvarez PA, Ponte ML, Bellosu WH, Bagnes C, Gonzalez CD et al. Drug-induced QTc interval prolongation: A multicentre study to detect drugs and clinical factors involved in every day practice. Curr Drug Saf; 2015; 23:345-56.
18. Pasquier M, Pantet O, Hugli O, Pruvo E, Buclin T, Waebber G et al. Prevalence and determinants of QT interval prolongation in medical inpatients. Intern Med J. 2012; 42(8):933

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