ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 5, pp. 16886-16889, May, 2017

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

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

Ashkan Nejati., Hemraj Singh and Alireza Naghdi

[1]Department of Pharmacy, Karnataka College of Pharmacy, Karnataka State, India
[2]Department of Pharmacy, Sumandeepvidyapeeth University, Gujarat State, India

DOI: http://dx.doi.org/10.24327/ijrsr.2017.0805.0237

ARTICLE INFO

Article History:

Received 15th February, 2017
Received in revised form 25th March, 2017
Accepted 23rd April, 2017
Published online 28th May, 2017

ABSTRACT

Objective: The present study is aimed to assess drug induced QT-interval prolongation in hospital inpatients through ECG data, 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 prescription. 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. ***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 us 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.

INTRODUCTION

The QT interval is measured on the electrocardiogram (ECG) and represents the ventricular depolarization and repolarization (Niemeijer 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

Corresponding author:* **Ashkan Nejati
Department of Pharmacy, Karnataka College of Pharmacy, Karnataka State, India

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 corrected 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

Unaccepted 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 study by Vandael E *et al* conducted at 6 psychiatric hospital in Flanders, Belgium (Vandael E *et al*, 2014). The demographic 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

	Gender					
						Total
Parameter	Male		Female			
	n	%	n	%	n	%
Patient age (Years)						
20-30	4	3.63	8	7.27	12	10.90
31-40	2	1.81	16	14.54	18	16.36
41-50	13	11.81	7	6.36	20	18.81
51-60	2	1.81	10	9.09	12	10.90
61-70	12	10.90	13	11.81	25	22.72
71-80	12	10.90	5	4.54	17	15.45
81-90	2	1.81	4	3.63	6	5.45
Sub total	47	42.72	63	57.27	110	100
Special population						
Geriatric	27	24.54	29	26.36	56	50.91
Renal impairment	1	0.9	3	2.72	4	3.63
Sub total	28	25.45	32	29.09	60	54.54
Co-morbidities						
Diabetes Mellitus	19	17.27	20	18.18	39	35.45
HTN	17	15.45	19	17.27	36	32.72
CKD	1	0.9	1	0.9	2	1.81
Pulmonary Disorder	5	4.54	6	5.45	11	10
CNS Disorder	5	4.54	3	2.72	8	7.27
Hypothyroidism	4	3.63	2	1.81	6	5.45

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 Switzerland30. 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

Table 3 Primary diagnosis and QTc interval

Diagnosis	Total number	Prolonged 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)
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 Pick ham *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 Mean±SD(n) Total=60	QT prolonged-n(%) or Mean±SD(n) Total=50
Age(110)	50.58(60)	51(50)
Male(47)	23(48.97)	24(51.03)
Female(53)	37(58.73)	26(41.27)
Reason for admission		
Respiratory	10	2
Hemodynamic	17	35
Neurologic	4	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±13.56(50)
Potassium(90)	3.8±1.2(44)	3.6±1(46)
Calcium(50)	4.5±1.4(20)	4.3±1.2(30)
Magnesium(67)	2.3±1.4(30)	2.1±1.3(37)
Creatinine(40)	1.03±1.3(15)	1.4±1.1(25)
Glucose(70)	146.3(30)	148.9(40)
Arrhythmias(10)	2	8
HR on ECG()	104±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 (Curtis 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 (Viktil 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 Ivabradine 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. About 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

predictor of drug induced QT-interval prolongation (Pickham D *et al*, 2012).

Table 5 Top 5 common pDDI

pDDI pair	Male		Female		Total	
	n	%	n	%	n	%
Ondansetron/Metronidazole	21	17.21	20	16.39	41	33.60
Ondansetron/Ciprofloxacin	7	5.73	8	6.55	15	12.29
Ciprofloxacin/Metronidazole	3	2.45	10	8.19	13	10.65
Metronidazole/Promethazine	2	1.63	5	4.09	7	5.73
Ondansetron/Promethazine	3	2.45	2	1.63	5	4.09

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 fornon-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. Isbister GK. Risk assessment of drug-induced QT prolongation. *Aust Prescr*. 2015; 38:20-4.
9. Vandael E, Marynissen T, Reyntens J, Spriet I, Vandenberghe 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, Hutchison 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, Reikvam 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, Belloso 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, Pruvot E, Buclin T, Waeber G *et al*. Prevalence and determinants of QT interval prolongation in medical inpatients. *Intern Med J*. 2012; 42(8):933

How to cite this article:

Ashkan Nejati., Hemraj Singh and Alireza Naghdi.2017, A Prospective Study on Assessment of Drug Induced Qt Interval Prolongationin Inpatient Department At A Tertiary Care Hospital. *Int J Recent Sci Res.* 8(5), pp. 16886-16889.
DOI: http://dx.doi.org/10.24327/ijrsr.2017.0805.0237

****