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ORIGINAL RESEARCH

Evaluating the patients on predefined subset of drugs and its association with QTc prolongation

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Abstract

Introduction: Drug-induced QT prolongation is the most common cause of acquired QT prolongation. Risk factors for QTc prolongation and TdP are recorded as the following: female sex, old age, cardiac disease, electrolyte abnormalities, diabetes mellitus type II, thyroid disease, and bradycardia. Hence the present study was conducted to find out the changes in QTc readings after taking predefined subset of drugs among patients.

Materials and Methodology: This study is adopted as a prospective observational study and was planned to be conducted at L.N. Medical College & Research centre and associated J.K Hospital Bhopal. . The study group was formed based on the fulfilment of the inclusion and exclusion criteria. There are certain biochemical tests to be done in order to exclude the acquired cause. The primary test to be followed is ECG in which the QTc was calculated, measured and analysed. Baseline ECG was recorded at the time of inclusion then follow up ECG was recorded within 24 hours of completion of antibiotic treatment, and 7 days of antidepressant and antipsychotic treatment.

Results: Theoverall distribution of study subjects according to level of QTc change according to drug class results revealed that maximum 64 subjects those were on antibiotics, 49 subjects were on antidepressants and 40 subjects were on anti-psychotics where QTc level change 1-5ms.There were significant ($p<0.01$) association of various drugs class with according to level of QTc change.

Conclusion: Acquired QTc prolongation due to drugs is the most common cause for QTc prolongation observed in clinical practice. Though antipsychotics, antidepressant and antibiotics could cause significant QTc prolongation, ventricular tachycardia or Torsade De Pointes is more common with simultaneous use of two or more other QT prolonging drugs.

Keywords: QT elongation, drug-induced, anti-psychotics, anti-depressants

Introduction

In the condition such as QTc prolongation, the delay in ventricular repolarization could possibly be resulted due to a reduction in the outward potassium current that leads to the broadening of ventricular action potentials.[1] QT prolongation might result in a diverse arrhythmic conditions, that include a major condition such as torsade de pointes, which is a type of ventricular tachycardia that is known to result in sudden cardiac death.[2]

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Drug-induced QT prolongation is the most common cause of acquired QT prolongation.[3,4] Furthermore, A drug's propensity to cause QT interval prolongation may cause its withdrawal from the market.[5] Accordingly, the early detection of drug-induced QT prolongation is crucial from the medical and socioeconomic perspectives. There are numerous studies have keenly studied the drug-induced QT prolongation, but most of these investigations have the following limitations. In many cases, researchers first select the drug to be investigated.[3,6]

Risk factors for QTc prolongation and TdP are recorded as the following: female sex, old age, cardiac disease, electrolyte abnormalities, diabetes mellitus type II, thyroid disease, and bradycardia.[7] Females are at higher risk of developing QTc prolongation than males; this is probably because of the hormone oestrogen which lengthens the QTc interval whereas the testosterone shows the evidence that shortens it.[8] Hyperglycaemia has an direct effect on cardiac repolarization and might contribute to a longer QTc interval or cardiac arrhythmia.[9] The QTc intervals normally reduces with tachycardia and lengthen with bradycardia. However, bradycardia is a risk factor for developing QTc prolongation.[4]

There are quite a few medications that are known to cause major prolongation of QTc. It is usually quantified that up to 3% of all the prescriptions are for potentially QTc prolonging medications.9 There are some non - cardiovascular drugs that have been recommended to be withdrawn from the commercial market that potentially cause an increase in the QTc interval of only 5–10 ms.[12] Most of the medications that can prolong the QTc interval block the IKr channel3 and can induce TdP sudden death in previously healthy adults. Hence the present study was conducted to find out the changes in QTc readings after taking predefined subset of drugs among patients.

Materials and methodology

This study is adopted as a prospective observational study and was planned to be conducted at L.N. Medical College & Research centre and associated J.K Hospital Bhopal. After obtaining the ethical approval from the institutional ethical committee, written consent was obtained from all the study subjects prior to the start of the study. The study group was formed based on the fulfilment of the inclusion and exclusion criteria. There are certain biochemical tests to be done in order to exclude the acquired cause. The primary test to be followed is ECG in which the QTc was calculated, measured and analysed. Baseline ECG was recorded at the time of inclusion then follow up ECG was recorded within 24 hours of completion of antibiotic treatment, and 7 days of antidepressant and antipsychotic treatment.

The QTc intervals were promptly measured from the start of Q to the end of T wave. The U wave was not considered in the measurement of QTc interval in our study. Heart rate directly affects the QT interval and various correction formulas are being employed to normalize it. All the collected data was analysed statistically using SPSS version 21 software in the form of percentages, proportions and are mostly represented as tables, charts, graphs wherever mandatory. Appropriate tests of significance were applied wherever necessary.

Results

Table 1 shows age group wise distribution of study subjects results revealed that out of 215 subjects maximum 91 belongs to 21-40 year age group, 79 belongs to 41-60 years , 14 subjects aged under 20 years and 31 subjects belongs to aged above above 60 years.

Table 2 shows gender-wise distribution of study subjects results revealed that 108 were female and 107 were male subjects.

Table 3 shows comparison of distribution of study subjects having prolonged QTc of different levels after medication according to drug after taking Azithromycin showed that 1 subject reported 6-10 ms and same number reported in 11-60 ms prolonged. After taking

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Clindamycin showed that 1 subject reported 0-5 ms and same number reported in 6-10 ms change. After taking Escitalopram showed that 1 subject reported 0-5 ms and same number reported in 6-10 ms change. After taking olanzapine showed that 2 subjects reported 11-60 ms. After taking Risperidone showed that 1 subject reported 11-60 ms and same number reported in >60 ms change. Comparison of distribution of study subjects having prolonged QTc of different levels after medication shows non significant (p=0.4).(

Table 4 shows Age group wise distribution of study subjects having QTc prolongation grouped according to drug class results revealed that QTc prolongation found in maximum 41-60 years age group subjects those who treated with Clindamycin, Escitalopram, Olanzapine and Risperidone.(Graph 13) Table 22 shows drug and comorbIdites wise QTc prolongation amond study subjects results revealed that there were 48 subjects of Pneumonia on Azithromycin out of them QTc prologation observed in 2 subjects , 35 subjects of Pneumonia on Clindamycin out of them QTc prologation observed in 2 subjects, 36 subjects of general anxiety disorder and painic attack which on Escitaloparam out them QTc prolongation was observed in 1-1 each,41 subjects of Bipolar affective disorder on Olanzapine out of them QTc prologation observed in 2 subjects 32 subjects of Bipolar affective disorder and schizopherenia which on Escitaloparam out them QTc prolongation was observed in 1-1 each.

Table 5 shows distribution of subjects having various grades of QTc prolongation after medication according to drug class results revealed QTc was prolonged in those4 subjects who were on antibiotics,2 subjects those were antipsychotics and 3 subjects were on anti-psychotics.

Table 6 shows overall distribution of study subjects according to level of QTc change according to drug class results revealed that maximum 64 subjects those were on antibiotics, 49 subjects were on antidepressants and 40 subjects were on anti psychotics where QTc level change 1-5ms.There were significant (p<0.01) association of various drugs class with according to level of QTc change.

Table - 1: Age group wise distribution of study subjects

Age Group (Years)	Frequency	Percent (%)
<20	14	6.5
21-40	91	42.3
41-60	79	36.7
>60	31	14.4
Total	215	100.0

Table - 2: Gender wise distribution of study subjects

	Frequency	Percent (%)
Female	108	50.2
Male	107	49.8
Total	215	100

Table - 3: Comparison of distribution of study subjects having prolonged QTc of different levels after medication according to drug

	0-5ms	6-10ms	11-60ms	>60ms

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	N	%	N	%	N	%	N	%
Azithromycin	0	0.0	1	50.0	1	50.0	0	0.0
Clindamycin	1	50.0	1	50.0	0	0.0	0	0.0
Escitalopram	1	50.0	1	50.0	0	0.0	0	0.0
Olanzapine	0	0.0	0	0.0	2	100.0	0	0.0
Risperidone	0	0.0	0	0.0	1	50.0	1	50.0
Chi square value	12.5							
p value	0.4							

Table - 4: Age group wise distribution of study subjects having QTc prolongation grouped according to drug class

Drug Name	Age group (Years)	Frequency	Percent (%)
Azithromycin	**21-40**	1	50.0
	>60	1	50.0
Clindamycin	**41-60**	1	50.0
	>60	1	50.0
Escitalopram	**21-40**	1	50.0
	41-60	1	50.0
Olanzapine	**41-60**	2	100.0
Risperidone	**41-60**	1	50.0
	>60	1	50.0

Table - 5: Distribution of subjects having various grades of QTc prolongation after medication according to drug class

Drug class	QTc prolongation grade	Frequency	Percent (%)
Antibiotics	**No prolongation**	79	95.2
	Prolonged	4	4.8
Anti-depressants	**No prolongation**	57	96.6
	Prolonged	2	3.4
Anti-psychotics	**No prolongation**	69	94.5
	Prolonged	3	4.1
	Severely prolongation	1	1.4

Table - 6: Overall distribution of study subjects according to level of QTc change according to drug class

	No change		1-5ms		6-10ms		11-60ms		>60ms	
	N	%	N	%		%	N	%	N	%
Antibiotics	11	13.3	64	77.1	7	8.4	1	1.2	0	0.0
Anti-depressants	0	0.0	49	83.1	10	16.9	0	0.0	0	0.0
Anti-psychotics	1	1.4	40	54.8	22	30.1	9	12.3	1	1.4
Chi square value	44.90									
p value	<<0.01*									

Discussion

Drug-induced QT prolongation is defined as a QTc of 500 ms or greater or an increase of 60 ms or greater in the QT interval compared with the premedication baseline interval.[10] There is

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an extensive list of medications that can prolong the QT interval. Many of these drugs are common in clinical practice, such as antiarrhythmics, antimicrobials, antipsychotics, antihistamines, and antiemetics.[11]

The results obtained by *Strle* F et al (2002) wherein there were 47 patients in which 31 were females and 16 were males.[12] Similar results were noticed in this present study considering the Gender wise distribution in the present study found that 108 (50.2%) were females and the remaining 107 (49.8%) were male subjects which clearly showed slight female predominance.

Arunachalam K et al (2018)[13]conducted a systematic review data were collected from PubMed and EMBASE databases were searched to identify studies reporting drug induced long QT syndrome and followed the PRISMA guidelines. Totally, 14,756 patients were exposed and 930 patients (6.3%) were found to have QTc prolongation.*Dhappili* R et al (2019)[14]compared the QTc interval in patients admitted as medical emergencies and to predict in-hospital outcomes of the patients. A total of 312 patients admitted in our hospital with acute medical emergency, the results revealed that Prolonged QTc interval was observed in 113 patients (36.2%).

Riad FSet al (2017)[15] determined the QTc prolongation has a high prevalence of and is associated with increased all-cause mortality. The rate of QTc prolongation was 71% versus 48% for men and 50% versus 34% for women, respectively. *Khan* Q et al (2019)[16] identified the total 487 drugs that prolong QTc. The most commonly used QT prolonging drugs in medical wards that were studied in the above study include azithromycin (4.7%), clindamycin (4.5%).

Results of the cohort study conducted by *Grewal* S et al (2020)[17] on 251 patients shows that the average baseline QTc in male patients was 441 ± 30 ms while maximum QTc during treatment (QTc max) was 476 ± 36 ms. For the female patients, mean baseline QTc of 438 ± 26 and QTc max of 468 ± 38 were observed. In the present study considering the change in level of QTc according to the drug, it has been found that the QTc level change 1-5 ms among maximum 12 female and 22 male among all subjects who were on azithromycin drug,18 female and 12 male among all subjects who were on clindamycin drug, maximum 15 female and 15 among all subjects who were on escitalopram drug, maximum 15 female and 15 among all subjects who were on escitalopram drug, maximum 15 female and 4 among all subjects who were on fluoxetine drug, maximum 19 female and 4 among all subjects who were on olanzapine drug.

Conclusion

Acquired QTc prolongation due to drugs is the most common cause for QTc prolongation observed in clinical practice. Though antipsychotics, antidepressant and antibiotics could cause significant QTc prolongation, ventricular tachycardia or Torsade De Pointes is more common with simultaneous use of two or more other QT prolonging drugs. However, the decision to initiate drug therapy should be based on a careful evaluation of the pre-existing comorbidities, risk factors of QT prolongation and concomitant medication use. More detailed randomized controlled studies with accurate description of baseline QTc, change in QTc interval and appropriate report of any significant ventricular arrhythmias with usage of multiple QTc prolonging drugs should be performed in future.

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