Prescribing Practices of QT Interval Prolonging Drugs in Critically Ill Older Adults in South India

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Citation

Moolambally SR, Malik A, Boloor A. Prescribing Practices of QT Interval Prolonging Drugs in Critically Ill Older Adults in South India. *Kathmandu Univ Med J.* 2023;83(3):298-303.

ABSTRACT

Background

It was Dissertenne who first described a cardiac phenomenon known as the Torsades de Pointes (TdP). QT prolongation caused by drugs is one of the most important causes for acquired QT prolongation syndrome.

Objective

To observe the prescribing practices of QT interval prolonging drugs among a high-risk population of critically ill older adults in a tertiary care hospital in South India The objectives were to identify the most commonly prescribed QT prolonging drugs, to analyse types of QT prolonging drugs based on risk of causing QT prolongation, to study the frequency of occurrence of common risk factors for QT prolongation and to identify presence of any significant relationships among the study variables.

Method

We have conducted a one-year cross-sectional descriptive study of the prescribing practices of QT interval prolonging drugs among 319 critically ill older adults in a tertiary care hospital in South India. Data was analysed to categorize the most common drugs which prolong QT interval; the type and frequency of use of QT interval prolonging drugs and to find the most common risk factors for QT prolongation in this study population.

Result

In this study, ondansetron, clarithromycin, azithromycin,and amiodarone were the most prescribed among the drugs with known risk of QTc (Corrected QT interval) prolongation. Among the drugs with conditional risk of QTc prolongation, pantoprazole, frusemide, piperacillin-tazobactam and esomeprazole were the most prescribed. The most common risk factors for QTc prolongation that were identified in this study were bradycardia, acute kidney injury, chronic kidney disease and low serum potassium.

Conclusion

This study helps to inform our physicians regarding the commonly prescribed QT interval prolonging drugs so that they may reduce co prescription of multiple QT prolonging drugs in high-risk patients. It identifies kidney injury, low potassium, and bradycardia as common risk factors for QT interval prolongation in these patients.

KEY WORDS

Long QT syndrome, Physician prescribing pattern, Torsades de pointes

INTRODUCTION

It was Dissertenne who first described a cardiac phenomenon known as the Torsades de Pointes (TdP).[1] TdP is a potentially fatal arrhythmia and is identified as a risk factor which can increase the risk of sudden cardiac death independent of other factors.[2] Advanced age, female gender, the presence of renal, cardiac, and hepatic failure are the common risk factors known to increase the risk of QT prolongation. QT prolongation caused by drugs is one of the most important causes for acquired QT prolongation syndrome.[3] Studies show that the awareness of drug induced TdP risk among healthcare professionals is low and is frequently overlooked in regular clinical practice.[4] Hence, we undertook a study to observe the prescribing practices of QT interval prolonging drugs among critically ill older adults. The risks of QT prolongation and the mortality associated with it, is greater among older adults.[5] The AZCERT (Arizona Centre for Education and Research), now known as the CredibleMeds®, is a non-profit organization which maintains a web-based list of drugs, known to cause QT prolongation and / TdP.[6,7]

The objectives of the study were to study the frequency of use of the most common QT interval prolonging drugs prescribed for critically ill older adults and to analyse types of QT prolonging drugs based on risk of causing QT prolongation. In addition, we have also studied the frequency of common risk factors for QT prolongation among the study subjects and attempted to identify significance of relationships among the study variables.

METHODS

We have conducted a cross-sectional time bound descriptive study of the prescribing practices of QT interval prolonging drugs among critically ill older adults. The study was conducted after obtaining ethical approval from Institutional Ethics Committee, Kasturba Medical College, Mangaluru (IEC KMC MLR 09-19/440). The study was done at a tertiary care teaching hospital in South India. The study duration was October 2019 to July 2021. It was a time bound study conducted for a period of 12 months and included data from 319 older adults(age > 60 yrs) admitted to the ICU during the study period. Data was collected by method of convenient sampling. The older adults who died or were discharged from the ICU in < 24 hours and patients admitted under surgical units (General Surgery, Orthopedics, ENT, OBG) were not included in the study. Following Institutional Ethics Committee approval all older adults admitted to the ICU during the study period were included in the study. Basic demographic details, diagnosis, and presence of known risk factors 6 for QT prolongation and / TdP were recorded according to a structured proforma. Data collection was done between 24 to 72 hours after admission into the critical care unit. For laboratory values, the hospital's laboratory standards were used to determine the values which were below the lower limit of normal. Hypokalaemia was defined as a potassium level of < 3.5 mEq/L, hypocalcaemia was defined as calcium level of < 8.5 mg/dL, hypomagnesemia was defined as magnesium level of < 1.8 mg/dL; blood urea was recorded as abnormal if it was > 40 mg/dL, and serum creatinine was recorded as high if it was > 1.4 mg/dL. The values for the above laboratory parameters were taken before the initiation of replacement therapy for potassium, calcium, or magnesium. ECG was recorded within 24 hours of admission in ICU and automated value of QTc was considered for analysis in the study. For the present study, the diagnosis of QTc interval prolongation was made if QTc interval was > 450 ms for females and > 440 ms for males. The formula which we have used in the current study is the Bazett's formula: QTc (ms) = QT interval (ms) / √RR interval (ms).[8] The crediblemeds.org website was used to classify drugs into the three categories based on their potential to cause QT prolongation and / TdP: namely known risk, possible risk, and conditional risk. The three risk categories according to crediblemeds.org were as follows.[6]

Known Risk of TdP: Substantial evidence supports the conclusion that these drugs prolong the QT interval and are associated with a risk of TdP when used as directed in the labelling.

Possible Risk of TdP: Substantial evidence supports the conclusion that these drugs can cause QT prolongation but there is insufficient evidence that the drugs, when used as directed in the labeling, have a risk of causing TdP.

Conditional Risk of TdP: Substantial evidence supports the conclusion that these drugs prolong the QT interval and are associated with a risk of developing TdP, but only under certain known conditions.

Data was analysed to categorize - the most common drugs which prolong QT interval, the type, the frequency of use of these drugs in this study population and to find the most common risk factors for QT prolongation. The demographic characteristics, length of stay, patient diagnosis, risk factors, and QTC prolonging drugs were analysed with respect to QTc interval. To ascertain statistical significance, the 2-sided chi-square test, or the fishers exact test (if n < 5) were calculated. Variables that were significant in univariate analysis were selected for multi-variate analysis by logistic regression method. Statistical significance was ascertained by fixing p-value < 0.05 for significance. Data was analysed using the IBM SPSS Statistics for Windows Version 25.0 Armonk, NY: IBM Corp.

RESULTS

In our study cohort (Table1), 319 patients were studied and we found that 56.4% (180/319) patients were males. 12.5% (40) patients succumbed to their illness after 24 hours of the ICU admission. Patients who died within 24 hours of

ICU admission were not included in the study. In this study, 89.6% (286/319) patients were between the age group of sixty to eighty years old. The risk factors (Table 3)for QTc prolongation which were most common in our study were hypertension (238/319), diabetes mellitus (161/319), acute kidney injury (93/319), low serum potassium (81/319), chronic kidney disease (47/319), ischemic heart disease (45/319). The most common diagnoses in our study population were pneumonia (178/319), obstructive airway disease (87/319), sepsis and septic shock (65/319), and cerebrovascular accident (46/319). It was observed that overall, 51.4% (164/319) patients in our study cohort had prolonged QTc interval. Also, in this study, we observed that 8.1% (26/319) of patients had QTc interval prolongation of > 500 ms. In our study cohort, another relevant observation is that several drugs classified in the CredibleMeds® lists were prescribed to most of the critically ill older adults at admission to the Intensive Care Unit. 90.5% (289/319) of patients in our study cohort received at least one QTc interval prolonging drug at the time of doing the electrocardiogram. We found that 45.4% (145/319) of the patients in our study were prescribed drugs with known risk of QTc prolongation / TdP. Another finding which is relevant is the use of multiple QTC interval prolonging drugs in our study cohort and 56.4% (180/319) received co-prescription of more than one QTC prolonging drugs on admission. In the present study (Table 4) ondansetron, clarithromycin, azithromycin and amiodarone were the most commonly prescribed among the drugs with known risk of QTC prolongation. Among the drugs with conditional risk of QTC prolongation, pantroprazole, frusemide, piperacillin-tazobactum and esmoprazole were the most prescribed (Table 4). Our study found that overall, proton pump inhibitors were the most commonly prescribed class of QTc interval prolonging drugs and 71.4% (228/319) patients were prescribed proton pump inhibitors. We also found that proton pump inhibitors were co-administered with diuretic (n=42), amiodarone (n=6), and antibiotic piperacillin tazobactam (n=45). Moreover, our study identified 42.3% (11/26) cases with QTc interval > 500 ms were prescribed with proton pump inhibitors. In our study cohort piperacillin tazobactam antibiotic was prescribed to 22.3% (71/319) patients. As it was co- prescribed with diuretics (n=45) in several patients,this could increase the cumulative risk of QTc prolongation. Univariate analysis was conducted between QTc prolongation and variables in the study. The odds ratio and 95% confidence interval for variables with significant p-values are as follows; male gender -1.80 (1.15-2.82), number of drugs ≥ 1 - 3.85 (2.40-6.14), hypothyroidism- 5.58 (1.20-25.9), sepsis -1.63 (1.12-2.36), chronic kidney disease -18.58 (5.63-61.29), acute kidney injury -17.03 (8.13- 35.68), bradycardia -2.34 (1.17-4.70), low serum potassium- 11.07 (5.44-22.54), high blood urea -25.94 (12.96-51.90), high serum creatinine -33.89 (14.91-77.02), ondansetron- 2.04 (1.08-3.84), clarithromycin -17.88 (2.34-135.59), amiodarone- 8.94 (1.12-71.43), frusemide -2.60 (1.50-4.49), and piperacillin tazobactam -1.87 (1.09-3.23). Pearson correlation coefficients (r) were calculated for continuous variable i.e., quantitative determinants of QTc interval prolongation. (Table 5) The p-values were significant for serum creatinine, blood urea, serum potassium, and number of drugs ≥ 1. In addition, multivariate analysis was performed by logistic

Table 1. Baseline characteristics of the study cohort

Patient characteristics and outcome		Total	Percentage
Gender	F	139	43.6
	M	180	56.4
	Grand Total	319	100
Age (years)	60 – 70	180	56.5
	71 - 80	106	33.2
	Above 80	33	10.3
	Grand Total	319	100
	Mean Age ± SD	69.78±10.72	
Outcome	Death	40	12.5
	Alive	279	87.5
	Grand Total	319	100.
Cause of death	Acute coronary Syndrome	1	
	Cerebrovascular Accident	3	
	ARDS, Pneumonia	4	
	Cardiac arrest	4	
	Envenomation	1	
	Heart failure Aortic stenosis	1	
	Hepatic encephalopathy Decompensated Chronic Liver disease	1	
	Sepsis or septic shock	23	
	Severe Dengue	1	
	Upper gastrointestinal bleed	1	
Length of stay (days)	1 – 4 days	221	69.3
	5 – 10 days	72	22.6
	Above 10 days	26	8.2
	Grand Total	319	100
Mean QTC duration ± SD (ms)	450.46±36.99		

Table 2. Frequency of use of QTC prolonging drugs

QTc and drugs received		Total	Percentage
QTc interval duration	Abnormal	164	51.4
	Normal	155	48.6
	Grand Total	319	100
Number of QTc prolonging drugs	0	30	9.4
	1	109	34.2
	2	120	37.6
	3- 5	60	18.8
	Grand Total	319	100

Table 3. Risk factors for QT prolongation

Risk Factors (RF)	RF Present	Age %	RF Absent	Age %	Total	Age %
Diabetes Mellitus	161	50.5	158	49.5	319	100
Hypertension	218	68.3	101	31.7	319	100
Coronary Artery Disease	33	10.3	286	89.7	319	100
Arrhythmia	27	8.5	292	91.5	319	100
Heart Failure	36	11.3	283	88.7	319	100
Ischemic Heart Disease	45	14.1	274	85.9	319	100
Congestive Heart Failure	3	0.9	316	99.1	319	100
Chronic Kidney Disease	47	14.7	272	85.3	319	100
Acute Kidney Injury	93	29.2	226	70.8	319	100
Bradycardia	42	13.2	277	86.8	319	100
Low Serum Potassium	81	25.4	238	74.6	319	100
Low Serum Calcium	48	48.9	50	51.0	98	100
Low Serum Magnesium	20	36.4	35	63.6	55	100
High Blood Urea	120	37.9	199	62.1	319	100
High Serum Creatinine	108	34.6	211	65.4	319	100

Table 4. Frequency of prescription of drugs with Known risk, Possible risk and Conditional risk

Drugs Having Known Risk of QTC Prolongation (1)	Prescribed	Age %
Ondansetron	50	15.7
Azithromycin	43	13.5
Clarithromycin	18	5.6
Amiodarone	10	3.1
Domperidone	9	2.8
Fluconazole	6	1.9
Amphotericin B	2	0.6
Levofloxacin	2	0.6
Voriconazle	2	0.6
Escitalopram	1	0.3
Hydroxychloroqune	1	0.3
Ciprofloxacin	1	0.3
Drug Having Possible Risk Of QTC Prolongation (2)	**Prescribed**	**Age %**
Ofloxacin	2	0.6
Drugs Having Conditional Risk Of QTC Prolongation (3)	**Prescribed**	**Age %**
Pantoprazole	158	49.5
Frusemide	77	24.1
Piperacillin Tazobactam	71	22.3
Esomeprazole	70	21.9
Ivabradine	7	2.2
Metronidazole	5	1.6
Ranolazine	4	1.3
Oseltamevir	1	0.3
Atazanavir/Ritonavir	1	0.3
Amitrytaline	1	0.3
Efavirenz	1	0.3
Quetiapine	1	0.3
Dothiepin	1	0.3
Olanzapine	1	0.3

Table 5. Pearson Correlation Coefficients between continuous variables and QTC Interval Duration

Variable	Pearson (r)	P-value
Age	0.025	0.655
Serum Creatinine	.276**	<.001
Blood Urea	.344**	<.001
Serum Potassium	-.259**	<.001
Number of drugs ≥ 1	.196**	<.001
Serum Calcium	-.176	0.083

Table 6. Multivariate analysis by logistic regression for variables with dichotomy

Variables	B	S.E.	Sig.	Exp(B) Adjusted Odds ratio	95% C.I. for EXP(B)	
					Lower	Upper
Acute Kidney Injury	3.279	.488	<.001	26.543	10.204	69.047
Chronic Kidney Disease	2.716	.722	<.001	15.122	3.675	62.233
Number of drugs (≥1)	1.949	.387	<.001	7.021	3.289	14.989
Male Gender	.397	.345	.250	1.487	.756	2.925
Bradycardia	1.178	.497	.018	3.248	1.226	8.602
Low Serum Potassium	3.062	.456	<.001	21.360	8.732	52.251
Constant	-3.161	.426	<.001	.042		

regression of dichotomous risk factors of drug induced long QTcsyndrome (Table 6). In this analysis the adjusted odds ratio and confidence interval for the variables wereanalysed p-value was found to be significant for acute kidney injury, chronic kidney disease, number of drugs ≥ 1, bradycardia, and low serum potassium.

DISCUSSION

This was a cross sectional study of prescribing practices of QT prolonging drugs among physicians who were prescribing for older adults admitted to the ICU. It was observed that more than half of the study cohort had a prolonged QT interval at baseline with 8.1% having a QT interval of > 500 ms which was comparable to several similar studies. In a study conducted by Rossi et.al, 9 it was

found that 11.9% of their study population had QTc interval prolongation of > 500 ms. An Israeli study showed that 7.15% had QTc interval prolongation of > 500 ms.[10] Another French study found that 5% had QTC interval prolongation of > 500 ms.[11]

In this study a large proportion of patients (90.5%) were prescribed with at least one QTC prolonging drug during ICU admission. A similar observation was also found in a study conducted by Pasquier et al., the study showed that more than half of the patients received at least one QTC prolonging drug during hospital stay.[12] In a study conducted by Rossi et al. it was found that, almost 66% (160/243) received a prescription of more than one QTc interval prolonging drug.[9] Both the studies classified drugs as per CredibleMeds® list. We also noticed that a very commonly prescribed QT prolonging drug in this study was proton pump inhibitor. Other drugs such as macrolide antibiotics and amiodarone were also commonly prescribed here.

Prescription of QTc interval prolonging drugs along with proton pump inhibitors may increase the risk of drug-drug interactions and can be a contributory factor in the adverse outcome for critically ill older adults admitted in ICU. Another finding of our study is that diuretic (furosemide) is the second most common QTc prolonging drug prescribed in our study cohort. Diuretics are prescribed commonly for cardio-renal failure and can cause hypokalaemia and hypomagnesemia, which cause an additional increase in the risk of QT prolongation.[13]

In a study conducted by Rossi et al. significant p-values were found for male gender, bradycardia, hypocalcemia, hypothyroidism, heart failure, and use of QT-prolonging drugs.[9]

In a research article by Lubart et al. it was observed that prevalence of QTc interval prolongation in males was statistically significant as compared to females.[14] Rautaharaju et al. also identified that elderly males have a greater slope for QTc interval prolongation as compared to elderly females.[15]

While we have not studied actual causation of QT prolongation in this study, we have discovered large volume of prescription of drugs with known risk and conditional risk among older adults who seem to be at high risk of Torsades de pointes due to coexistence of multiple drugs related and unrelated factors and presence of other risk factors for QT prolongation. Studies have revealed that such combinations do not necessarily cause arrhythmia in all patients.[16] The risk of arrythmias depends on the specific combinations of drugs and risk factors. However, it still is important for physicians to be aware of the AZCERT classification and to be cautious while prescribing such drugs.[16] QT prolongation may have been pre existing in the study population or may have been caused by other risk factors such as low potassium or renal injury, thereby the addition of drugs may not have an etiological association for the ECG changes which were recorded at baseline. The drugs identified in this study reflect a preponderance for antibiotics and also the clinical risk factors reflect underlying septicemia or multiorgan failure which is often the most common diagnosis in ICUs in our part of the world and hence may be a reflection of the clinical case profile rather than of prescribing practices. Nevertheless, this remains a real world study of prescribing practices recorded in a tertiary care setting in South India.

The primary objectives of this cross-sectional study were to identify the risk factors and analyze the prescription practices for critically ill older adults admitted in ICU. The study identified the common risk factors and QTc interval prolonging drugs prescribed in our study cohort. Our study cohort received proton pump inhibitors, diuretics, antibiotics, anti-arrhythmic, anti-depressant, and anti-psychotic medications which had the risk of QTc interval prolongation associated with its use as per the database maintained by CredibleMeds®. The most common risk factors for QTC prolongation that were identified among older adults in this study were bradycardia, acute kidney injury, chronic kidney disease, low serum potassium, and use of QTc prolonging drugs.

The study was done at a single tertiary care center and was a cross-sectional study without followup for a possible cardiac event during ICU stay. In this study, Bazett's formula was used for QTc interval prolongation which is assumed to overcorrect QT intervals at a faster heart rate. In the present study, QTc interval was considered prolonged in males if it was greater than 440 ms and it was considered prolonged in females if it was greater than 450 ms. The QTc prolongation standard could have overestimated the patients with prolonged QTc interval. In addition, some laboratory parameters were not available for all the patients in our study and that would have underestimated the effect of variables like low serum calcium and low serum magnesium. The present study did not analyse QTc interval prolongation after taking into consideration drug-drug interaction. The drug-drug interaction would probably shed further light on effect of drugs on QTc interval prolongation.

CONCLUSION

In our study cohort, the number of patients with QTc interval prolongation > 500 ms was 8.1%. We found that QTc prolonging drugs were commonly used on admission to ICU (45% of patients received drugs with a known risk of QTC interval prolongation). We found that proton pump inhibitors and diuretics were most frequently prescribed to the study cohort population. This study helps to inform our physicians regarding the commonly prescribed QT prolonging drugs and to review their prescriptions for QT prolonging drugs especially in case of critically ill older adults with kidney injury, low potassium, and bradycardia.

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