QT INTERVAL PROLONGATION WITH ESCITALOPRAM

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ABSTRACT:

BACKGROUND: *QT interval prolongation is one of the most feared adverse effects of Escitalopram (SSRI).The objective of the study was to quantify the impact of escitalopram on corrected QT interval (QTc) which is a risk marker for life threatening ventricular arrhythmia.*

AIMS & OBJECTIVE: *To quantify the impact of escitalopram on corrected QT interval (QTc).*

MATERIAL & METHODS: *This descriptive case series was done on three hundred consecutive patients (Age: 20-70 years) reporting with depression at psychiatry department of Services hospital, Lahore between 1st January 2018 to 30th June 2018. Written informed consent was taken and study was approved by ethical review committee. Resting ECG and transthoracic echocardiogram of all patients were done and QTc interval calculated using Bazett method. Baseline investigations including renal profile, liver function tests and serum electrolytes were also done. All patients were started on escitalopram (5mg). Patients already on any antidepressant or QTc prolonging drug, baseline QT prolongation (> 500ms), cardiac patients and patients with abnormal rhythm on ECG were excluded. Patients were followed up monthly for 6 months and dose of antidepressant was adjusted accordingly. At the end of six months patients were called for re-enrollment. Two hundred and sixty patients were found eligible for the study who were then divided into four categories depending upon the dose of antidepressant drug (5,10,15 and 20mg). Average increase of QTc interval was then calculated in each category.*

RESULTS: *Among 260 patients, regarding mean age grouping and distribution was 5mg dose (52.62 ± 9.46 years), 10mg dose (50.52 ± 9.40 years), 15mg dose (52.62 ± 9.46 years) and 20 mg dose (50.52 ± 9.40 years); p value 0.283. Serum Potassium; 5mg dose (3.8mmol/L), 10mg dose (4.0mmol/L), 15 mg dose (3.9mmol/L) and 20mg dose (3.9mmol/L); p value 0.361.Serum Magnesium; 5mg dose (1.9mg/dl), 10mg dose (1.9mg/dl), 15 mg dose (2.1mg/dl) and 20mg dose(1.9mg/dl); p value 0.301. Serum calcium; 5mg dose (9.0mg/dl), 10mg dose (8.7mg/dl), 15 mg dose (8.9mg/dl) and 20mg dose(8.9mg/dl); p value 0.431. Baseline QTc; 5mg dose (414ms), 10mg dose (391ms), 15 mg dose (399ms) and 20mg dose(402ms); p value 0.212. Mean QTc prolongation; 5mg dose (3.8ms), 10mg dose (6.2ms), 15 mg dose (8.9ms) and 20mg dose(13.4ms). Maximum QTc prolongation in 5mg dose (4.7ms), 10mg dose (8.8ms), 15 mg dose (13.9) and 20mg dose (21.8ms).*

CONCLUSION: *QT prolongation with escitalopram alone in non-cardiac normal QT patients is not significant enough to endanger the patient to life threatening ventricular arrhythmia.*

KEYWORDS: *Escitalopram, QT interval, arrhythmias, electrocardiogram*

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INTRODUCTION:

Escitalopram is the most widely used antidepressant in Pakistan and QTc prolongation is its most feared complication. Torsades de pointes, a life threatening type of ventricular arrythmia may be precipitated by prolongation of QTc Interval.[1] Citalopram and escitaopram both are enlisted in medium risk category of QTc prolonging antidepressants.[2] They differ marginally in terms of their risk of prolonging the QTc and this prolongation is dose-dependent.[3] QTc prolongation by escitalopram at higher dosages is almost comparable to prologation by citalopram.[3]

Corrected QT interval is a better indicator of QT as it takes heart rate into account. Bazett method is the most widely used formula for QTc calculation.[4] Normal QTc interval in males is less than 430ms while in females it is less than 450ms.[4] Escitalopram is usually avoided if QTc is greater than 500ms.[4] The magnitude of QTc prolongation appears to be greater for citalopram than escitalopram, but the dose-QTc correlation is almost similar for both drugs.[5] Healthcare Products Regulatory Agency in the United Kingdom has issued safety warnings for both the drugs.[5] In one study, 14% of patients with escitalopram overdoses presented with QTc interval prolongation.[6] The proportion of prolonged QTc interval associated with escitalopram overdoses (1.7%) was comparable to that with citalopram overdoses (3.7%). [6]

The QTc interval greater than 500 ms or longer or a change from baseline of 60 ms or more should alert the physician.[6,7] Caution is advised if QT is between 450-500ms. But sometimes physicians are overcautious even at much lower level of QT interval. This has resulted in increased hospital stay and increased dosage of benzodiazepines and related drugs to the patients.

QTc prolongation mostly in cases of escitalopram use is multi-factorial with effect of escitalopram being multiplied by use of concomitant drugs or conditions. Drug dosage is only one of several factors that increase the risk of QTc interval prolongation. Established risk factors for QTc prolongation include advanced age, existing cardiac or medical illnesses, electrolyte disturbances and concomitant use of other QTc-prolonging drugs.[9] Risk factors have been emphasized in the regulatory warnings to physicians. Physicians should have knowledge of these risk factors when prescribing medicines.

The objective of the study was to quantify the impact of escitalopram on corrected QT interval (QTc) in Pakistani population to help out the physicians in prescribing correct dosage to the patients. Moreover this study will help out the physicians in follow up of patients on escitalopram.

MATERIAL AND METHODS:

This was a descriptive case series done on three hundred consecutive patients (Age: 20-70 years) reporting with depression for first time at psychiatry department of Services hospital, Lahore between 1st January 2018 to 30th June 2018. Written informed consent was taken and study was approved by ethical review committee. Demographic and clinical data were collected. Depression was diagnosed on the basis of International classification of diseases (ICD-10) criteria. Detailed history especially of any cardiac ailment was taken from each patient. Resting ECG and transthoracic echocardiogram of all patients were done and QTc interval calculated using Bazett method. Baseline investigations including renal and liver function tests and serum electrolytes (Sodium, Potassium, Magnesium & Calcium) were also done. All patients were started on escitalopram (5mg). Exclusion criteria included patients already on any antidepressant drug or on any QTc prolonging drug, baseline QT prolongation (> 500ms), known cardiac disease and patients with abnormal rhythm on ECG.

Two hundred and sixty patients were then divided into four categories depending upon the dose of antidepressant drug. Eighty patients were taking 05 mg escitalopram while 81 were taking 10mg escitalopram. Thirty one were on 15mg and 68 were on 20 mg escitalopram. Average increase of QTc interval was then calculated in each category.

Patients were followed up monthly for 6 months and on each visit patients were completely evaluated for symptoms & QT prolongation and dose of antidepressant were adjusted accordingly. Baseline investigations including renal and liver function tests, serum electrolytes (Sodium, Potassium, Magnesium & Calcium) were repeated monthly.

At the end of six months patients were called for re-enrollment. 278 patients responded. Out of 278 patients 08 had stopped antidepressants on their own while 10 had been following at some other psychiatry clinic. None of patients had any cardiac event during these 06 months.

Statistical Analysis: The analysis was performed using SPSS V 16.0 for windows. Quantitative data was expressed as mean value ± standard deviation. Qualitative variables were presented by calculating frequency and percentage. Data was stratified for antidepressant dose. Baselines characteristics were compared by t-test. Baseline QT, QT prolongation and serum electrolytes were compared using Mann-Whitney U test. P value less than 0.05 was considered statistically significant.

RESULTS:

Among 260 patients; Mean age; 5mg dose (52.62 ± 9.46 years), 10mg dose (50.52 ± 9.40 years), 15mg dose (52.62 ± 9.46 years) and 20 mg dose (50.52 ± 9.40 years); p value 0.283. Oldest patient was of 67 years while youngest was of 20 years. Gender; 5mg dose (Male:33 Female:47), 10mg dose (Male:28 Female:53), 15 mg dose (Male:12 Female:19) and 20mg dose(Male:30 Female:38); p value 0.220. Serum Potassium (Normal Lab range: 3.5 – 5.5 mmol/L); 5mg dose (3.8mmol/L), 10mg dose (4.0mmol/L), 15 mg dose (3.9mmol/L) and 20mg dose (3.9mmol/L); p value 0.361. Serum Magnesium(Normal Lab range: 1.9-2.5mg/dl); 5mg dose (1.9mg/dl), 10mg dose (1.9mg/dl), 15 mg dose (2.1mg/dl) and 20mg dose(1.9mg/dl); p value 0.301. Serum calcium (Normal Lab range: 8.5 -10.5 mg/dl); 5mg dose (9.0mg/dl), 10mg dose (8.7mg/dl), 15 mg dose (8.9mg/dl) and 20mg dose(8.9mg/dl); p value 0.431.

Baseline QTc; 5mg dose (414ms), 10mg dose (391ms), 15 mg dose (399ms) and 20mg dose(402ms); p value 0.212. Mean QTc prolongation; group wise distribution was 5mg dose (3.8ms), 10mg dose (6.2ms), 15 mg dose (8.9ms) and 20mg dose(13.4ms). Maximum QTc prolongation in 5mg dose (4.7ms), 10mg dose (8.8ms), 15 mg dose (13.9) and 20mg dose (21.8ms).(Table-1)

Table-1:

	Escitalopram+ Dose (mg)				P value
	5.0	10.0	15.0	20.0	
Age	52.62 ± 9.46	50.52 ± 9.40	52.62 ± 9.46	50.52 ± 9.40	0.283
Gender	Male:33 Female:47	Male:28 Female:53	Male:12 Female:19	Male:30 Female:38	0.220
Serum Potassium (mmol/l)	3.8	4.0	3.9	3.9	0.36
Serum Magnesium (mg/dl)	1.9	1.9	2.1	1.9	0.301
Serum Calcium (mg/dl)	9.0	8.7	8.9	8.9	0.431
Baseline QTc (ms)	414	391	399	402	0.202
Mean QTc Prolongation (ms)	3.8	6.2	8.9	13.4	-
Max. QTc Prolongation (ms)	4.7	8.8	13.9	21.8	-

DISCUSSION:

In this descriptive case series, QTc prolongation was quantified for different drug dosages of escitalopram in psychiatric patients. QTc prolongation with use

of escitalopram as monotherapy was not clinically significant even at high dose of the drug.

Psychiatric patients are more prone to cardiovascular problems compared to non-psychiatric patients.[10,11] Mortality rates are also higher in psychiatric patients than in the general population[12] and the adverse effects of pharmacological treatment is regarded as one the major cause of high mortality.[13]

Among SSRIs, citalopram and escitalopram are categorized in medium risk group while sertraline, fluoxetine and paroxetine are in low risk group in regard to QTc prolongation.[14]

The effect of a single antipsychotic drug on QTc interval has been reported in several large scale trials. In one study mean QTc increase with citalopram was found to be 8.5ms for 20mg dose while it was 12.6 for 40mg and 18.5 for 60mg dose while for escitalopram it was 4.5 for 10mg dose, 6.6ms for 20mg dose and 10.7 for 30mg dose.14 These results are comparable to our results with mean QTc increase of 3.8ms with 5mg dose, 6.2ms with 10mg dose, 8.9ms with 15 mg dose and13.4ms with 20mg dose.

QTc is most commonly obtained through Bazett's formula. Prolongation of the QTc interval by any drug is considered a good marker of the arrythmogenic potential of that agent. Any QTc above 500 ms requires discontinuation of the medication, while dose reduction is necessary with intervals of 470 to 500 ms in males and 480 to 500 ms in females.[15,16] QTc interval prolongation can occur starting from day 5 of treatment to after 30 days of treatment.[17]

QTc interval is prolonged by a number of factors like female gender, advanced age, concurrent use of more than one drug that can prolong QT interval, Electrolyte disturbance (hypokalemia, hypomagnesaemia and hypocalcaemia), renal dysfunction, bradycardia, congenital long QT syndrome (LQTS), cardiac disease such as heart failure, left ventricular hypertrophy and myocardial infarction, baseline QT prolongation.[5] Drugs including antiarrhythmic drugs,antihistamines, antipsychotic and antidepressant agents neuroleptics, atypical antipsychotics,antidepressants, antibiotics, antimalarials,antiprotozoal antifungal and antimotility agents all can increase QTc interval.[5]

Psychiatric population treated with antipsychotic monotherapy had much less risk of developing an increase in QTc interval compared to those treated with antipsychotics plus an antidepressant.[18]

Psychiatric patients in addition to getting more than one QTc prolonging drug also frequently show electrolyte imbalances[18] therefore monitoring of the QTc interval before and after the beginning of treatment is essential, especially for patients taking multiple psychoactive drugs with QTc prolonging potential.

Prescribing a drug combination with two QTc prolonging drugs is not advisable.[1]

The synergic blockade of the HERG potassium channels and the increase in drug levels due to metabolic interactions are the two mechanisms suggested to be the reason of QT prolongation.[19]

Significant QT prolongation may occur through drug interaction when the combination therapy is given for a brief period, such as adding antibiotics[20] to antidepressants. Moreover, the patient at risk show reduced repolarization reserve.[21,22]

Before starting an antidepressant, thorough medical history, laboratory monitoring, and a baseline electrocardiogram (ECG) may be necessary to identify patients at risk for QT prolongation. Trinkley and colleagues[16] recommended that patients taking QT prolonging antidepressants with one or more risk factors should be monitored more closely with ECGs and electrolyte panels every month for the first 6 months and monitored once every 6 to 12 months thereafter.

QT prolongation risk also varies with each antidepressant. Beach and colleagues[15] observed that SSRIs, fluoxetine and paroxetine, are not statistically significantly associated with QT prolongation. This is not true with escitalopram and citalopram. Increase in QTc in case of escitalopram is less than the increase associated with usual doses of citalopram.[15]

Amitriptyline and maprotiline are tricyclic antidepressants that lead to QT prolongation, while other including clomipramine do not.[15] SNRIs, including duloxetine and desvenlafaxine[17] do not increase QTc while Venlafaxine do so. Bupropion and mirtazapine in usual doses are considered safe.

The association between escitalopram and ventricular arrhythmias and mortality has not been verified in studies but risk exits.[23] QT prolongation reflects the risk potential for an event to occur.[23]

Discontinuing escitalopram and starting another antidepressant is not always advisable in patients who are responding well to the medication because it can worsen the primary disease.

In our study of 13.4ms increase associated with 20 mg of escitalopram, may not be clinically significant alone but in combination with another drug or condition it can lead to catastrophe. So

treatment decisions must be individualized taking every individual as different from others.

CONCLUSION:

In conclusion, this study has shown that QT prolongation with escitalopram alone in non-cardiac normal QT patients is not significant. Dose reduction or selecting an alternative antidepressant in patients stable on escitalopram just out of fear of QTc prologation can prove dangerous. Antidepressants are not without risks but risk of QTc prolongation can be minimized by proper selection and monitoring of the drug.

The limitations of the study were that study population was in limited number, study conducted on depression patients only and that too only for 06 months. It would also be interesting to follow up patients for a longer period of time and with comparison of drug plasma levels.

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