INVESTIGATION OF THE CLINICAL SIGNIFICANCE OF ESCITALOPRAM-INDUCED ELECTROCARDIOGRAPHIC CHANGES IN MEN: A PILOT OBSERVATIONAL STUDY

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ABSTRACT

Objective: We sought to investigate the clinical significance of secondary electrocardiographic (EGC) changes in men after using escitalopram.

Methods: This pilot observational cohort study recruited male patients taking escitalopram for at least 6 mo in Mental Hospital of Qassim. All patients underwent a 12-lead ECG examination. We also measured the heart rate (HR), QTc, and QRS interval. Data on all related medical conditions and medications were recorded.

Results: Fifty-three men were recruited, with a mean age of 37.39±8.39 y: 34.4% and 31.1% of these patients were taking escitalopram for depression and anxiety, respectively. The mean dose of escitalopram was 14.35 mg. Observations showed that 20.9% of the patients taking escitalopram had a fast HR (>100 beats/min [bpm]), indicative of sinus tachycardia, whereas 11.4% of patients had a slow HR (<60 bpm). The mean QT and QTc in patients taking escitalopram were 366.6±228.69 and 398.92±16.15 ms, respectively.

Conclusion: Low doses of escitalopram resulted in minimal clinically significant changes. Thus, patients should be monitored when doses are escalated further.

Keywords: Selective serotonin reuptake inhibitors, Anxiety disorders, Electrocardiography, Corrected QT, Heart rate, Tachycardia, Depression

INTRODUCTION

Escitalopram is the S-enantiomer of citalopram, which is available in strengths of 5, 10, and 20 mg, and it is prescribed for several psychiatric conditions, such as major depressive disorder and generalized anxiety disorder [1]. Escitalopram may be involved in a series of several drug-to-drug interactions, such as QT prolongation, nodal rhythm, ventricular arrhythmias, and torsade de pointes, which may potentiate the magnitude of its cardiotoxicity [2]. As escitalopram is metabolized by cytochrome enzymes, such as CYP3A4 and CYP2C19, variability in responses should be expected [3].

Although escitalopram is considered to be less cardiotoxic than citalopram, several studies have considered the effect of escitalopram on the heart, particularly in terms of QT prolongation, the most obvious electrocardiographic (EGC) feature of patients who have been treated, and particularly overdosed, with escitalopram [4–7]. The threshold of clinical significance of corrected QT (QTc) is 500 milliseconds (ms) or a change in the baseline of 60 ms [4].

Consensus has not yet been reached with regard to these abnormalities [9]. However, several studies have evaluated citalopram with regard to its cardiotoxicity [9–11]. Such studies have shown that citalopram may induce almost double the prolongation of QTc than that by escitalopram at an equivalent therapeutic dose. Therefore, 20 mg of citalopram and 10 mg of escitalopram (the equivalent therapeutic dose) may cause QT prolongation of 8.5 and 4.5 ms, respectively [12]. Escitalopram has also been repeatedly reported to prolong the QT interval, although the clinical significance of this effect is still under debate [7, 13]. Furthermore, several official agencies have reported the same issue. For instance, a 10-mg and a 30-mg dose of escitalopram would be expected to cause changes from baseline of 4.3 ms (confidence interval [CI]: 2.2–6.6) and 10.7 ms (CI: 8.6–12.8), respectively [14]. Another study reported a similar prolongation of 2-5 ms in cases of chronic kidney disease (CKD) [15]. Several other selective serotonin reuptake inhibitors (SSRIs) have been reported to exert a similar impact on the heart. Furthermore, the risk of prolongation may increase in patients with CKD, those aged>60 y, and with use of antipsychotic and tricyclic at high doses [15–17].

An earlier study analyzed the plasma levels of escitalopram and attempted to correlate these data with QTc changes. However, no correlation was found, and only the use of antipsychotic and tricyclic agents was found to be associated with QTc prolongation [17]. This finding may be justified by the fact that several other confounding variables, such as liver function, multiple genetic alleles, QT baseline, and the magnitude of drug-drug interactions, exert an effect. Consequently, the clinical sequelae of this type of prolongation may not be well correlated [18].

Consequently, there are insufficient data in existing literature to relate changes in QTc to the use of escitalopram and the clinical consequences of such changes [8]. Therefore, in the present study, we sought to investigate the clinical significance of ECG changes, particularly in QTc, in patients taking escitalopram with no known cardiac diseases.

MATERIALS AND METHODS

This pilot observational cross-sectional cohort, phase one study was conducted in the Mental Hospital of Qassim (ethical approval number 20170511). It was conducted in accordance with the principles of the Helsinki Declaration. The sample size required for a pilot study was estimated to be 50 patients. The inclusion criteria were as follows: adult men of Saudi nationality, those prescribed escitalopram for at least 6 mo for any psychiatric or medical illnesses, and those who agreed to be part of the research and provided informed consent. We excluded all patients who were diagnosed with any form of cardiac disease, had a history of ECG changes, or those who were taking other medications that might cause ECG changes aside from their psychiatric...
medications, as these may have an impact on the accuracy and validity of our results.

All patients received a 12-lead ECG examination using a standard approach. QT (ms) intervals were measured on lead II from the beginning of the Q wave to the end of the T wave. All QT intervals on lead II were used to calculate the mean QT duration for each ECG. Patients’ pulse rate (PR) was taken using an auto-measure ECG strip. Normal heart rate ranges from 60 to 100 beats per minute; any value above this range was considered to represent tachycardia, whereas any value below this range was considered to represent bradycardia. The QTc was calculated automatically by the ECG reader. The QTc is considered a cardiac risk factor if it is recorded as >0.43 for male patients and 0.45 for female patients. QRS intervals were measured for all ECG examinations by taking the mean duration for all QRS intervals in lead II. A normal duration was ±0.12 seconds; values higher than this normal duration were considered abnormal.

RESULTS

Two hundred patients who presented with a range of psychotic disorders were screened for eligibility. This study included only 53 patients who met the inclusion criteria. The mean dose of escitalopram was 14.35 mg. All patients were men, and their mean age was 37.39±8.39 years. Escitalopram was indicated for either their primary problem or additive therapy, as follows: major depressive disorder (37%), anxiety disorders (27.78%), schizophrenia (18.52%), and additive management (16%). Besides escitalopram, 34.4% and 31% of the patients were taking other medications for depression and anxiety, respectively (table 1).

| Name of co-administered medications | Number of patients |
|-------------------------------------|--------------------|
| Risperidone                         | 6                  |
| Mirtazapine                         | 6                  |
| Aripiprazole                        | 3                  |
| Amisulpride                         | 3                  |
| Quetiapine                          | 2                  |

Most of our patients (71%) had a normal heart rate. However, 18% of patients taking escitalopram had a relatively fast heart rate of >100 beats/min (range: 101-110), indicative of sinus tachycardia, whereas 11% of the patients had a slow heart rate of <60 beats/min (range: 50-75; table 2). The cohort with bradycardia was prescribed only escitalopram. The mean QT of patients taking escitalopram was 366.62±28.69 ms, whereas the mean QTc was 398.92±16.15 ms. The mean PR interval was 159.45±25.35 ms; mean QTc was 96.40±9.94 ms, and mean heart rate was 80±15.88 beats/min.

DISCUSSION

SSRIs are commonly used to treat a range of psychiatric and medical disorders, and they are considered effective and relatively safe [19, 20]. However, some concerns about the cardiotoxicity of SSRIs have recently been raised [21]. As escitalopram is one of the most commonly used SSRIs, it is essential to confirm whether they are associated with cardiac-induced ECG abnormalities [22]. Generally, research has shown that escitalopram will reduce one’s heart rate by 2 beats/min and prolong the QTc by 3.5 ms and that such changes are independent of the dose [23].

Escitalopram is known to exert similar side effects as citalopram [24, 25]. However, escitalopram exhibits higher serotonergic toxicity and less cardiac toxicity than citalopram [6]. Although escitalopram is considered less cardiotoxic than citalopram, several studies have demonstrated the effects of escitalopram on the heart, and particularly QT prolongation, as this is the most obvious ECG feature of patients who have been treated with escitalopram, especially an overdose of escitalopram. Most of the reported cases of toxicity occurred in patients taking doses that ranged from 20 to 560 mg (median = 140 mg) and included varied symptoms, such as bradycardia, prolonged QT interval, and serotonin toxicity syndrome. Other serious effects were reported when other medications were co-ingested along with escitalopram [13]. It is, therefore, wise to closely monitor both QRS and QTc in patients who have experienced an overdose [26]. There have been no deaths or seizures reported from the ingestion of only escitalopram. Following at least 6 mo of escitalopram administration, our patients did not show any significant increase in either QTc or QRS; both of these indices were within the normal range. Evaluating QTc at baseline and then again at 6 mo post-therapy may be more useful diagnostically.

Escitalopram has been shown to increase the risk of tachycardia or bradycardia in addition to QTc abnormalities [6, 7, 23]. Tachycardia may also present in cases of co-ingestion with other medications rather than a sole treatment induced by only escitalopram [23]. Patients may also develop QT-HR abnormalities, which may be considered a risk for torsades de pointes [6, 27]. In our present study, 18% and 11% of patients presented with tachycardia and bradycardia, respectively, although none of the patients developed prolonged QTc that was above the normal range. Therefore, the risk of torsade de pointes was minimal or nil. Surprisingly, bradycardia developed in only patients who were taking escitalopram alone. Hence, further monitoring of such patients is essential. Generally, escitalopram is considered a relatively safe choice with minimal ECG changes, provided that the dose used remains within the clinical ranges. Adding further medications, however, may lead to complications.

There are some limitations to our study that need to be considered. First, this study did not report baseline ECG data before the initiation of escitalopram. Second, the results may not be generalizable because of the nature of metabolic single nucleotide polymorphisms in Saudi patients, which may influence the way
escitalopram is metabolized. However, recording baselines and monitoring ECGs may be judicious.

CONCLUSION
Escitalopram seems to be safe in low doses and cause mild clinical changes on one's heart rate. Higher doses should be studied further to confirm the Food and Drug Administration warnings regarding QTc changes.

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AUTHORS CONTRIBUTIONS
Dr. Ahmad Almeman is the principal investigator, and he designed and followed the study protocols. Anas Alkhwiri, Ebrahim Alsalf, Rakan Alahmad, and Azzam Alyahya were the team responsible for data collection, analysis, and manuscript writing. Dr. Nabil Alruwaisn and Dr. Mansour Alhabri are psychiatrists who assessed the needs for escitalopram and followed the patients in the hospital during the study period. Dr. Basem Almogbel was responsible for the inclusion and exclusion criteria. Dr. Akram Eldesokey is the cardiologist who evaluated the electrocardiographic changes.

CONFLICTS OF INTERESTS
We declare no conflict of interest.

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