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Research Article / Araştırma Makalesi

Evaluation of the Citalopram Levels on Qtc Interval in Rats Using with Radio-Telemetry

Sıçanlarda Sitalopram Düzeylerinin Qtc Aralığı Üzerine Etkilerinin Radyo-Telemetri Yöntemi ile Değerlendirilmesi

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Abstract

Long QT syndrome is an arrhythmogenic disease characterized by prolonged QT interval. Citalopram (CIT) was reported to prolong QT interval dose-dependently. Omeprazole (OMP), inhibits CIT metabolizing enzyme CYP2C19, thereby increases serum concentrations which may increase the risk of QT prolongation. These are commonly co-prescribed and recent studies have raised the safety concerns about. We aimed to investigate the dose dependent effects of citalopram alone and in combination with OMP. Forty male, Sprague Dawley rats were divided into 5 groups (n=8). CIT (10 mg/kg or 30 mg/kg) was given for 2 weeks alone or in combination with OMP (100 mg/kg) starting from the 2nd week. ECG recordings and blood samples were collected. QT interval significantly increased in all groups compared to control. The plasma level of CIT in the CIT30 group was significantly higher than CIT10 group ($p<0.01$) and was significantly higher in the CIT10+OMP group than that of the CIT10 group ($p<0.01$). In treatment groups, the increase in plasma citalopram level correlated positively with the increase in QT ($r=0.844$, $r2=0.713$). It was determined that CIT caused prolongation of QT interval, the addition of OMP increased QT interval more, and these increases correlated positively with CIT plasma concentration. Therefore, it would be appropriate to routinely measure CIT plasma levels in addition to ECG, particularly in patients with additional risk factors for QT prolongation.

Keywords: Citalopram, electrocardiography, long qt syndrome, radiotelemetry, therapeutic drug monitoring

Özet

Uzun QT sendromu, senkop ve ani ölüme neden olabilen QT aralığında uzama ile karakterize aritmojenik bir hastalıktır. Seçici serotonin geri alım inhibitörü olan sitalopram (CIT), en çok reçete edilen antidepresanlardan biridir. CIT'nin doza bağlı olarak QT aralığını uzattığı bildirilmektedir. Bir proton pompası inhibitörü olan omeprazol (OMP), CIT metabolize edici enzim CYP2C19'u inhibe eder, böylece CIT'nin serum konsantrasyonunu artırır ve bu da QT uzaması riskini artırabilir. CIT ve OMP genellikle birlikte reçete edilir ve son çalışmalar CIT ile OMP'nin birlikte kullanılmasıyla ilgili güvenlik endişelerini ortaya çıkarmıştır. Bu çalışmanın amacı, sıçanlarda sitalopramın tek başına ve OMP ile kombinasyon halinde QT aralığı üzerine olan etkilerini doza bağlı olarak araştırmaktır. Kırk adet erkek, Sprague Dawley sıçan 5 gruba ayrıldı (n=8). CIT 10 mg/kg ve 30 mg/kg 2 hafta süreyle oral gavaj yoluyla verildi, 2. haftadan itibaren de iki gruba OMP (100 mg/kg) ile kombine olarak verildi. Kontrol grubu sadece serum fizyolojik aldı. Birinci haftanın ve ikinci haftanın sonunda EKG kayıtları yapıldı ve kan örnekleri alındı. QT aralığı tüm gruplarda kontrol grubuna göre anlamlı olarak arttı. CIT30 grubundaki ilaç plazma düzeyi, CIT10 grubundan önemli ölçüde daha yüksekti ($p<0.01$). CIT10 + OMP grubunda CIT10 grubuna göre anlamlı derecede yüksekti ($p<0.01$). Tedavi gruplarında, plazma sitalopram düzeyindeki artış, QT aralığındaki artışla pozitif korelasyon gösterdi ($r = 0.844$, $r2 = 0.713$). Sitalopramın sıçanlarda QT aralığının uzamasına neden olduğu, metabolizma inhibitörü OMP eklenmesinin ise ilaç plazma düzeyini daha da arttırdığı. dolayısıyla QT aralığını da daha fazla arttırdığı gösterildi. Ek olarak QT aralığındaki artışların CIT plazma düzeylerindeki artışlar ile pozitif korelasyon gösterdiği belirlendi. Bu nedenle, özellikle QT uzaması için ek risk faktörleri olan hastalarda EKG takibinin ve CIT plazma düzeylerinin rutin olarak ölçülmesinin uygun olacağı görüşündeyiz.

Anahtar Kelimeler: Elektrokardiyografi, radyotelemetri, sitalopram, terapötik ilaç düzeyi izlemi, uzun qt sendromu

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1. Introduction

The QT interval is measured from the beginning of the QRS complex to the end of the T wave and it refers to ventricular depolarization and repolarization (1, 2). LQTS is an arrhythmogenic disease characterized with QT prolongation that can cause syncope and sudden cardiac death secondary to cardiac arrhythmias (3). LQTS is usually caused by mutations in genes that encode ion channels in the heart, however, some drugs, like selective serotonin reuptake inhibitors (SSRIs) can also lead to LOTS (4, 5). One of the most common reasons for the withdrawal of drugs or the restriction of use in recent years has been the prolongation of the QT interval (6, 7). Due to serious drug-induced arrhythmias, regulatory authorities require investigation of the possible risks of drugs to QT interval prolongation (8, 9). Selective serotonin reuptake inhibitors (SSRIs) are similar in efficacy to tricyclic antidepressants, but have high selectivity and low risk of side effects (10, 11). In recent years, some SSRIs have drawn attention due to their arrhythmogenic effects resulting in LOTS (12-15). Citalopram is one of the most frequently used is reported to alter the electrical activity of the heart, causing abnormal heart rhythm (12, 16). Citalopram is metabolised via CYP2C19 and Omeprazole (OMP), a proton pump inhibitor (PPI), can inhibit CYP2C19 (17). Omeprazole has shown to increase citalopram concentrations in humans (14). A study examining geriatric inpatient health records has reported that citalopram and omeprazole were commonly co-prescribed in this age-group which resulted in significant interactions causing QT interval prolongation of individuals (18).Moreover, a recent cohort study has reported that citalopram and omeprazole use increased incidence of sudden cardiac arrest in an Asian population as compared with non-users and this risk was also more pronounced in concomitant use (19). The radio-telemetry system is a method for evaluating the arrhythmogenic effects of drugs. The advantages of the system are that biological parameters can be measured in the closest conditions to physiological conditions, there are no time-dependent limitations, more than one biological parameter can be recorded simultaneously and continuously, there is no stress related to movement restriction or the physiological response due to general anesthesia is not suppressed, and the number of animals used can be reduced (20). In this study, we aimed to evaluate the effects of citalopram alone and in combination with omeprazole on QT interval using radio-telemetry method and relation of QT interval to plasma levels of citalopram in rats.

2. Material and Methods

Ethical Statement

This study was approved by the Local Ethical Committee for Animal Experimentation (Approval no: (25.01.2018/517).

Animals

Forty male, Sprague Dawley rats (250-300g, n=8 per group) were purchased from Medical and Surgical Research Center of our university and housed in a temperature (20–25°C) controlled room with a 12:12-h light-dark cycle with food and water ad libitum.

Experimental Procedures

Rats received 10 mg/kg or 30 mg/kg citalopram alone (Sigma-Aldrich, USA) for 2 weeks (CIT10 and CIT30 groups) or in combination with OMP (100 mg/kg, Sigma-Aldrich, USA) starting from 2nd week (CIT10+ OMP and CIT30+ OMP groups) via daily oral gavage at same time (10:00 am). Control rats received vehicle saline.At the end of the first week, the radio-telemetry transmitters (C50-PXT or F40 model, DSI, St. Paul, MN, USA, Ponemah software v6.50) were implanted as previously described(21) to perform electrocardiography (ECG) recordings in conscious freely moving rats (22). Briefly, transmitters were placed into the peritoneal cavity and electrodes were placed subcutaneously at the forefoot level under ketamine (80 mg/kg) and xylazine (10 mg/kg) anesthesia (20). Rats received intraperitenoal tramadol hydrochloride (25 mg/kg) for postoperative analgesia. After surgery, rats were housed individually. During one-week recovery period, Citalopram alone treated rats continued to receive citalopram

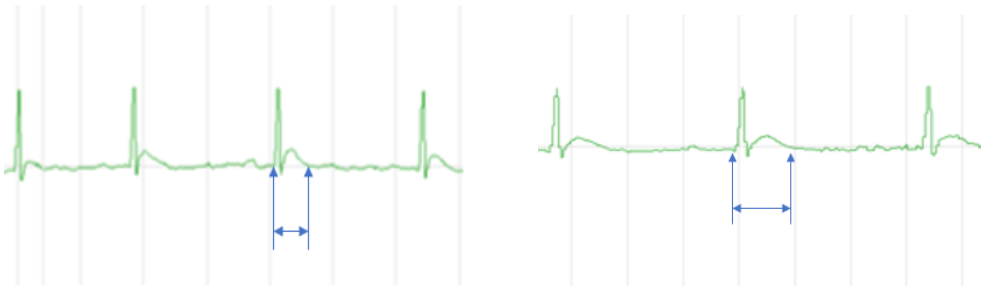
and omperazol combination groups of citalopram started to receive omperazol (CIT10+OMP and CIT30+OMP groups). ECG data were collected at 1000 Hz in 6 consecutive periods, each consisting of 10 min (at the and of first and second week). Bazett's equation is used for correction of prolongation of QT (23-25). Corrected QT interval (QTc) was to compare QT values according to heart rates and evaluate the risk of arrhythmia (26, 27). Plasma citalopram levels were measured at the end of the first week of treatment in the omeprazole-added groups and end of the second week of treatment in the all treatment groups. Blood samples were collected from the tail vein by using a strainer. The level of citalopram in plasma was measured by LC-MS/MS method. At the end point, rats were euthanized with high dose anesthetic and cervical dislocation.

Statistical Analysis

SPSS 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used to analyze the data. Measurement data were expressed as mean ± SEM. Data were analyzed by the One-Way ANOVA test followed by posthoc analyses with Tukey test. Regression correlation analysis was performed for the relationship between drug levels and QT intervals. $p < 0.05$ was considered statistically significant.

3. Results

All recordings (normal and prolonged QT intervals) were made by the radio telemetry system both as ECG image and numerically (Fig.1).



Normal QT (220ms) **Prolonged QT (255 ms)**

Fig 1. ECG images of normal and prolonged QT interval recorded by radiotelemetry system

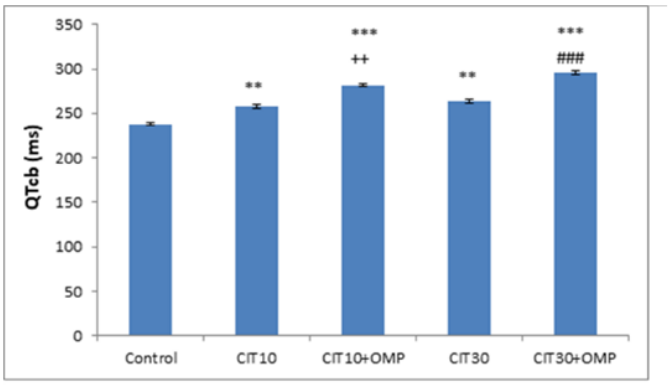


Fig 2. QT interval measurements in control and treatment groups(ms).
***p<0.01, *** p<0.001; vs. control group*
++ p<0.01; vs. CIT10 group
p<0.001; vs. CIT30 group;

QT interval was 237.91 ± 1.89 ms in the control group and 257.70 ± 2.18 ms in the CIT10 group; 281.84 ± 1.89 ms in the CIT10 + OMP group; It was increased to 264.06 ± 2.02 ms in the CIT30 group and 295.38 ± 2.18 ms in the CIT30 ± OMP group. Briefly, QT interval in CIT10, CIT10+OMP, CIT30 and CIT30+OMP groups was significantly increased compared to the control group ($p<0.01$, $p<0.001$, $p<0.01$ and $p<0.001$, respectively). On the other hand, addition of omeprazole increased the QT interval significantly in CIT10-treated and CIT30-treated animals ($p<0.01$ and $p<0.001$, respectively) (Fig.2).

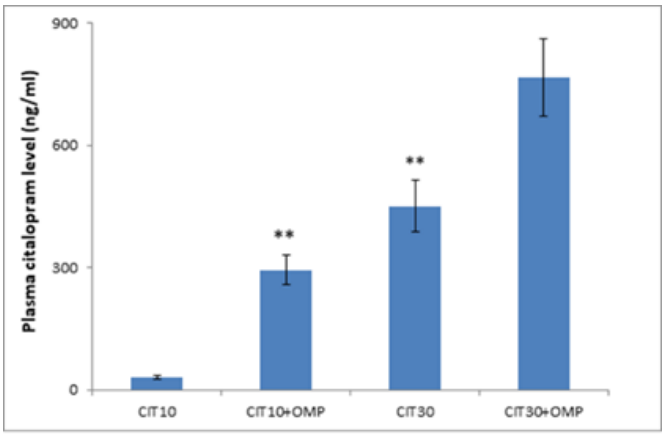


Fig. 3. Citalopram plasma levels (ng / ml) measured in treatment groups
**; $p<0.01$ vs. CIT10 group

Plasma citalopram level was measured in the treatment groups and a statistically significant difference was observed between the groups. Accordingly, citalopram plasma level in the CIT30 group was significantly higher than in the CIT10 group (451.00 ± 63.90 vs 30.79 ± 4.51 ng / ml) ($p<0.01$). Citalopram plasma level was also significantly higher in the CIT10 + OMP group compared to the CIT10 group (293.71 ± 36.09 vs 30.79 ± 4.51 ng / ml) ($p<0.01$). Although the citalopram plasma level in the CIT30 + OMP group increased slightly compared to the CIT30 group, this difference was not statistically significant (765.57 ± 94.77 vs 451.00 ± 63.90 ng / ml) ($p>0.05$) (Fig. 3).

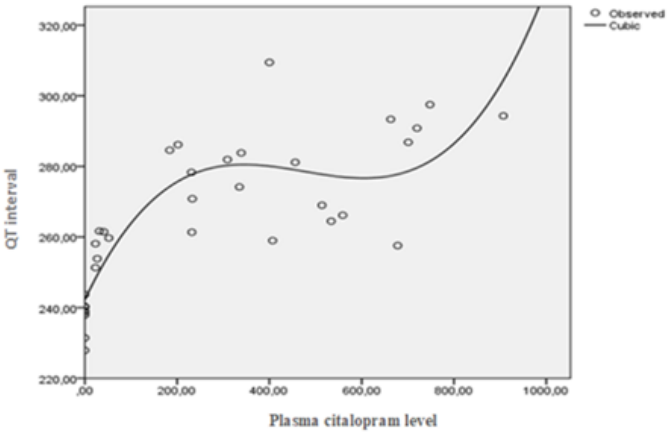


Fig. 4. Relationship between Citalopram plasma levels and QT interval values
($r = 0.84$, $r^2 = 0.713$)

The increase in citalopram plasma level in the treatment groups was positively correlated with the increase in QT interval value in the same groups (r = 0.844, r2 = 0.713) (Fig. 4).

4. Discussion

In our study, two different doses of citalopram (10 and 30 mg/kg) were given to rats alone or in combination with omeprazole (100 mg/kg) and QT interval were evaluated by telemetric method and plasma drug levels were measured.

As a result, citalopram plasma level increased according to the dose and QT interval prolonged in correlation with this. The addition of omeprazole to the treatment also resulted in a greater increase in both plasma drug level and QT interval compared to citalopram-alone administration. Accordingly, in a retrospective study, citalopram produced a dose-dependent increase in QT interval compared to baseline ECG results. The authors have recommended taking caution and frequent ECG follow-up visits during high dose citalopram use particularly in elder and high-risk patients with arrhythmia (28). In 2011, the FDA reported that citalopram doses should be limited to 40 mg/day as well as should be contraindicated in LQTS patients (21). Thereafter, in 2012, the FDA changed the definition of contraindications from not recommended to an absolute contraindication in patients with QT interval of over 500 ms (29). These warnings are based on a randomized, double-blind, placebo-controlled multicenter study (12). In addition, some studies with high doses use and some case studies with therapeutic doses has also reported prolongation of the QT interval (30-36). On the other hand, there are also some studies showing no negative effect on QT interval (37, 38). Mechanism of prolonging the QT interval has been suggested to be associated with direct blocking of cardiac potassium channels encoded by the human ether related gene (hERG) (39) and blocking of α L-type calcium channels (40-42). LQTS may be congenital or acquired abnormality and risk factors for acquired have been identified. For instance, female sex, advanced age, hypokalemia and hypomagnesemia; also combination with hepatic enzyme inhibitors (43-45). In our study, QT interval was significantly prolonged in omeprazole-added groups compared to citalopram-alone groups. So, FDA recommended limiting the maximum dose of citalopram to 20 mg/day in patients taking the CYP2C19 inhibitor (12). Accordingly, in our study, concurrent use of omeprazole and citalopram increased plasma citalopram level as well as QT interval. In a study reported that there was a significant increase in citalopram plasma levels when used with PPIs, and that a dose reduction of up to 50% may be required in patients (14). In a study conducted in healthy volunteers, omeprazole administration resulted increase citalopram concentration (46). In our study, increased doses caused an increase in both QT interval and plasma citalopram level with a positive correlation between these two parameters. This correlation was evaluated in order to determine whether routine plasma citalopram level measurement is required in patients using citalopram, particularly in those at high-risk for QT prolongation. There is no recommended drug plasma concentration range that can be used to evaluate the clinical response to citalopram treatment (47, 48), with only one case report suggesting that there may be a therapeutic window for citalopram in some patients (49). However, according to the results of our study, the increase in the dose of citalopram was directly related to both plasma drug level and QT interval. Therefore, we believe that monitorization of plasma level may be useful when used in combination with ECG follow-up in patients. Determination of a therapeutic window for citalopram plasma level may enable us to predict the high-risk patients before occurance of arrythmic ECG changes and to timely reduction of citalopram dose in this group of patients.

There are some limitations that need to be addressed in this study. Although the animals used were similar in terms of age and body weight, the basal heart rate, QT interval, electrolyte levels, and liver and kidney function were not evaluated. However, since young adult healthy male animals were used, it can be assumed that they did not have an

additional risk factor for QT prolongation in terms of these parameters.

In conclusion, in our study, it was found that 10 mg/kg and 30 mg/kg citalopram use caused prolongation of QT interval in rats, addition of omeprazole to the treatment further increased QT interval and these increases were positively correlated with citalopram plasma level. Therefore, we believe that it is appropriate to measure citalopram plasma level in combination with ECG recording routinely, particularly in patients with additional risk factors for QT prolongation. In the light of these results, further and larger animal and even human studies on the relationship between the QT interval and citalopram plasma level may provide stronger evidence about the necessity of measuring citalopram level.

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Ethical Statement

All experiments were performed with the permission of Eskisehir Osmangazi University Animal Experiments Local Ethics Committee (25.01.2018/517).

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