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Original Article

Evaluation of arrhythmic effects of clarithromycin usage in patients with acute coronary syndrome via new parameters of 12 lead electrocardiography

Akut koroner sendromlu hastalarda 12 ledli elektrokardiyografi yeni parametreleri kullanılarak klaritromisinin aritmik etkilerinin değerlendirilmesi

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Abstract

Aim: Clarithromycin is a widely used macrolide antibiotic with arrhythmic effects causing torsade de pointes by elongating QT interval. Clarithromycin was used to treat acute coronary syndrome. we aimed to determine the acute effects of short-term clarithromycin treatment on novel ECG parameters in patients with acute coronary syndrome.

Material and Methods: The study we conducted in 2002 evaluated the effects of clarithromycin on endothelial functions and QTdispersion. We recently analyzed these patients' ECGs performed before and one week after of 1000 mg/day clarithromycin treatment. We analyzed newly recognized parameters; Tp–e interval, Tp-e/QTc ratio, maximum QTc, minimum QTc, QTc dispersion values, P-maximum, P-minimum and P-wave dispersion to indicate the risk of atrial and ventricular arrhythmias.

Results: There were 40 patients included where 20 were treated with clarithromycin and 20 not. In the clarithromycin group, mean age of the patients was 53.2±8.0 and in control group 58.9±11.6. Demographic characteristics of patients were similar. All ECG parameters were comparable prior to clarithromycin treatment. However, following therapy, all parameters including max QTc, min QTc, QTc dispersion, Tp-e interval, TP-e/QTc, Pmax, Pmin, and P-wave dispersion were statistically significantly higher in clarithromycin treated group ($p<0.05$ for each).

Conclusion: Clarithromycin treatment not only affects QT parameters but also novel ECG parameters Tp–e interval and Tp-e/QTc ratio showing the risk of ventricular arrhythmias. It also affects P-wave parameters and dispersion that shows risk of atrial arrhythmias. We may conclude that clarithromycin treatment increases both ventricular and atrial arrhythmic risk during acute coronary syndromes.

Key words: clarithromycin; arrhythmias; cardiac; acute coronary syndrome

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Öz

Amaç: Klaritromisin yaygın olarak kullanılan kardiyak aritmik etkileri olan, QT uzaması ile torsade de point' e sebep olan mikrolit antibiyotiktir. Eskiden akut koroner sendrom tedavisinde de kullanılmıştır. Bu çalışmanın amacı akut koroner sendromlu hastalarda kısa dönem klaritromisin kullanımının aritmik riski gösteren yeni EKG parametreleri üzerine olan etkisinin gösterilmesidir.

Gereç ve Yöntemler: 2002 yılında yürütülen akut koroner sendromu hastalarda 1000 mg/gün bir hafta klaritromisin tedavisinin endotel disfonksiyonu ve QT dispersiyonu üzerine olan etkilerinin gösterildiği çalışmanın EKG'leri geriye dönük olarak yeniden yeni EKG parametreleri için analiz edilmiştir. Atriyal ve ventriküler artmış aritmi riskini gösteren bu yeni EKG parametreleri; Tp–e interval, Tp-e/QTc oranı, maximum QTc, minimum QTc, QTc dispersionu, P-maximum, P-minimum ve P dalga dispersiyonu incelenmiştir.

Bulgular: 40 hasta çalışmaya dahil edilmiştir. 20 hasta klaritromisin tedavisi almış yirmisi almamıştır. Klaritromisin tedavisi alan gurupta ortalama yaş 53,2 ± 8,0'dır. Kontrol gurubunda 58,9 ± 11,6'dır. Demografik karakterler ve tedavi öncesi EKG parametreleri her iki gurup için benzerdir ve karşılaştırılabilir. Fakat tedavi sonrası max QTc, min QTc, QTc dispersiyonu, Tp-e interval, TP-e/QTc, Pmax, Pmin ve P dalga dispersiyonu istatistiksel olarak anlamlı bir şekilde klaritromisin ile tedavi edilen gurupta kontrol gurubuna göre yüksektir ($p<0.05$, her bir parametre için).

Sonuç: Klaritromisin tedavisi QT parametreleri yanı sıra yeni EKG parametreleri olan ve artmış ventriküler aritmi riskini gösteren Tp–e interval ve Tp-e/QTc oranını etkiler. Bununla birlikte atrial fibrilasyon artmış risk faktörü olan P-dalga parametreleri ve dispersiyonunu da etkiler. Tüm bu sonuçlardan akut koroner sendromlarda klaritromisin tedavisinin ventriküler ve atriyal aritmik riski arttırdığı çıkarılabilir.

Anahtar kelimeler: klaritromisin; aritmiler, kardiyak; akut koroner sendrom

Introduction

Avast number of drugs including some antibiotics causes prolongation of the QT interval and are associated with increased risk of ventricular arrhythmias like torsades de pointes (TdP) [1]. They play role in inhibition of the cardiac rapid delayed rectifier potassium current (IKr), which has major role in ventricular electrical repolarization. A well-known feature of these drugs correlated with acquired long QT syndrome and TdP is their ability to produce pharmacological inhibition of the activity of the "human Ether-a-go-go Related Gene"(hERG) potassium ion channel and its native cardiac equivalent IKr [2]. Macrolide antibiotics including clarithromycin have also been demonstrated to inhibit the hERG channel current (IhERG) [3, 4].

Chlamydia pneumonia infections are believed to play role in the pathogenesis of atherosclerosis via inflammatory pathways. Chlamydia pneumonia seropositive patients had four-fold higher risk than seronegative patients in occurrence of cardiovascular events Antibiotics like clarithromycin are used in treatment of acute coronary syndromes, because the cytokines and proteolytic enzymes can trigger inflammation. However, the results are not conclusive [5].Clarithromycin is a commonly used macrolide antibiotic also in treatment of chlamydia infections [6-8]. It may affect QT parameters such as Tp–e interval, Tp-e/QTc and P wave dispersion. The predisposition to ventricular arrhythmias in macrolide treatment has been demonstrated just via QT parameters. But the changes in other electrocardiographic parameters (Pmax, Pmin and P-wave dispersion) related to atrial arrhythmia risk are unknown[9]. We aimed to demonstrate of the predisposition of atrial and ventricular arrhythmia risk in clarithromycin treatment via these new and old parameters of ECG.

Material and Methods

In 2002, Gocer H. et al. conducted a study named " acute effect of short term clarithromycin treatment on endothelial function in patients with acute coronary syndrome" (5). Forty patients with acute coronary syndrome was studied then for documenting the effects of clarithromycin treatment where 20 were treated and 20 not. In clarithromycin group, patients received 1000 mg/day (2x500 mg) po in addition to standard β-blocker, conventional heparin, nitrate and statin therapy. A 12 lead ECG (AT-102, Schiller AG, and Baar, Switzerland) was recorded for every patient at admission to hospital and after one week of acute coronary syndrome treatment. Recordings were acquired at a paper speed of 50 mm/s, with

1 mV/cm standardization. We retrospectively re-analyzed the ECGs of patients and documented Tp–e interval, Tp-e/QTc ratio, maximum QTc, minimum QTc, QTc dispersion values, P-maximum, P-minimum and P wave dispersion.We improved our accuracy using calipers and magnifying lenses. The onset of the P wave was defined as the first atrial deflection from the isoelectric line, and the offset was the return of the atrial signal to the baseline. The maximum and minimum P wave duration were measured and their differences were defined as the P dispersion [10,11]. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for the heart rate using the Bazett formula: cQT=QT√(R–R interval) [12]. The Tp-e interval was defined as the interval between the peak and end of the T wave, measurements of the Tp-e interval were performed from precordial leads, and the Tp-e/QTc ratio was calculated from these measurements [13,14].

The study was conducted according to the latest version of Helsinki Declaration. The study protocol was approved by local ethics committee in 2002 and due to retrospective nature of the study and since same ECGs on that study were restudied, informed consent was waived.

Statistical Analysis

All results are expressed as the mean ± SD. Univariate analysis was performed using Student t-test. Categorical data were compared against a chi-squared distribution. Linear regression analysis was used to determine the relationship between continuous variables. A p value <0.05 was regarded as significant.

Results

In the clarithromycin group, the mean age of the patients was 53.2 ± 8.0 and in control group 58.9 ± 11.6. The male/female ratio was 9:11 in treated group and 12:8 in control. All demographic characteristics are depicted in Table 1 and all were comparable between groups. The Tp–e interval, Tp-e/QTc ratio, maximum QTc, minimum QTc, QTc dispersion values, P-maximum, P-minimum and P wave dispersion values prior to treatment are designated in Table 2 and were comparable. All the ECG measurements following treatment are shown in Table 3 where the Tp–e interval, Tp-e/QTc ratio, maximum QTc, minimum QTc, QTc dispersion, P wave dispersion, P-max and P-min were statistically significantly higher in clarithromycin treatment group-1 compared to standard therapy group (p<0.05 for each).

Table 1. Demographic Characteristics of Patients

	Treatment Group (n:20)	Control Group (n:20)	p-value*
Age (year)	53.2 ± 8	58.9 ± 11.6	0.37
Male/Female	9:11	12:8	0.39
Smoker	15 (75%)	16 (80%)	0.40
BMI (Kg/m2)	25 ± 4	26 ± 5	0.48
History of CAD	5 (25%)	7 (35%)	0.39
Previous Arrhythmia	3 (15%)	4 (20%)	0.36

*chi-square
BMI: Body mass index CAD: Coronary artery disease

Table 2. Comparison of the electrocardiographic parameters prior to therapy

	Treatment Group (n:20)	Control Group (n:20)	p-value*
Maximum QTc interval (ms)	199.7± 18.8	193.3± 14.6	0.260
Minimum QTc interval (ms)	95.8± 12.7	96.8± 11.2	0.340
QTc dispersion (ms)	72.0±31.0	73.0 ±30.0	0.420
Tp-e interval (ms)	70.65 ± 11.28	69.00 ± 11.26	0.646
Tp-e/QTc ratio	0.19 ± 0.04	0.24 ± 0.22	0.375
Pmax	197.25 ± 13.75	193.45 ± 27.81	0.587
Pmin	96.90 ± 7.71	93.65 ± 7.65	0.189
Pd	100.35 ± 18.23	99.80 ± 29.42	0.944

*Independent Samples t-test

Table 3. Comparison of the electrocardiographic parameters following clarithromycin therapy

	Treatment Group (n:20)	Control Group (n:20)	p-value*
Maximum QTc interval (ms)	299.7± 18.8	198.3± 14.6	< 0.001
Minimum QTc interval (ms)	293.8± 13.7	108.0 ± 13.2	<0.001
QTc dispersion (ms)	96.0 ±49.0	76.0 ±41.0	<0.001
Tp-e interval (ms)	91.35 ± 11.08	72.20 ± 10.26	0.000
Tp-e/QTc ratio	0.40 ± 0.15	0.22 ± 0.08	0.000
Pmax	297.50 ± 28.97	204.80 ± 21.29	0.000
Pmin	153.70 ± 39.62	95.80 ± 9.05	0.000
Pd	143.80 ± 36.55	109.00 ± 23.95	0.001

*Independent samples t-test

Discussion

Macrolide antibiotics prolong QT interval and increase QT dispersion via pharmacological inhibition of the activity of the IhERG and its native cardiac equivalent, the delayed rectifierIKr. Ventricular repolarization harmony is disturbedwhich leads to prolongationof repolarization phase of cardiac cycle and finally risk of ventricular arrhythmia increases [15,16]. However, multiple large retrospective clinical studies investigating the arrhythmic risk of the macrolides in practice have yielded conflicting results [17,18].

The surface 12 lead electrocardiogram is a common, practical medical tool used for predicting atrial and ventricular arrhythmogenic risk in daily clinical practice. The QT interval and its correction by heart rate (QTc), QT interval dispersion, and recently documented and published markers such as the Tp-e interval and Tp-e/QTc ratio have been proposed as markers for predicting the development of malign cardiac ventricular arrhythmias and recommended as alternatives for the risk stratification of sudden cardiac death in patients with several medical conditions [19,20]. One of these is the acute coronary syndromes and has been demonstrated to change the duration of the QT interval, increase repolarization heterogeneity as an increase in QT dispersion and prolong the duration of the maximum electrocardiographic QT interval. Several pathologicreasons have been proposed to be related with the prolongation of the QT interval secondary to acute myocardial ischemia: changes in the myocardial response to catecholamine and cholinergic stimulation, perturbation of calcium or potassium ion channels, or induction of changes in the intracellular hydrogen concentration.[19,20].

One of the mostimportant of these parameters is Tp-e/QTc which is a measure of spatial dispersion of ventricular repolarization [20, 21].

Prolonged P wave duration and increased P-dispersion have been showed as a marker for increased risk for atrial fibrillation characterized by inhomogeneous and discontinuous atrial conduction [22].

In this study, we tried to demonstrate the risk of atrial and ventricular arrhythmias in patientsusing clarithromycin during acute coronary syndromes with these new repolarization parameters in our study. We found that QTc, QT interval dispersion, P wave dispersion, Tp–e interval and T-e/QTc ratio can be used all together in clarithromycin using patients with acute coronary syndromes to define arrhythmia risk.We showed that, besides of old ECG parameters for indicating ventricular arrhythmia risk, newly described parameters like Tp–e interval and Tp-e/QTc have additional value. We also found that P dispersion is increased in the clarithromycin treatment group and it shows the increased risk for atrial fibrillation. But it should be taken into consideration that we did not observe any atrial or ventricular arrhythmia after clarithromycin treatment. We didn't try to evaluate clarithromycin's effect on acute coronary syndrome, because the role of antibiotics in acute coronary syndromes is debatable [23-25]. Also Clarithromycin has an inhibitor effect on cytochrome CYP3A4 and so should not be used with as statins that are extensively metabolized by that enzyme. Besides clarithromycin can interact with acute coronary syndrome treatment and can increase some arrhythmic effect of some drugs (15,16).

Conclusion

Antibiotherapy especially with macrolides requires close observation of ECG in acute coronary syndrome in the setting if the use of antibiotics are obliged. Other antibiotics rather than clarithromycin must be preferred. If the use of macrolides is mandatory, the close observation of the surface ECG with new parameters for atrial and ventricular arrhythmia (Tp–e interval and Tp-e/QTc, P-dispersion) must be performed during acute coronary syndromes.

Declaration of conflict of interest

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