Research Article / Araştırma Makalesi

Evaluating the Effects of Acute and Chronic Doxorubicin Administration on Cardiac Function Through Electrocardiographic Measurements

Akut ve Kronik Doksorubisin Uygulamalarının Elektrokardiyografik Ölçümler Aracılığıyla Kardiyak Fonksiyon Üzerine Etkilerinin Değerlendirilmesi

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Abstract

Background: The medications used to treat cancer can lead to cardiac problems, which restricts their use. Furthermore, the method these medications are taken seems to have an impact on varied outcomes. Therefore, this study aimed to examine whether administering doxorubicin (DOX) agent acutely and chronically has distinct impacts on the electrical activity of the heart.
Materials and Methods: Twenty-six male Wistar-Albino rats, weighing between 200-250 grams, were split into three groups: control group; no treatment was applied to animals (n=8), DOX acute group: a single dosage of 15.05 mg/kg of DOX was given at the end of the 3 weeks (n=8), DOX chronic group; which received an intraperitoneal (i.p.) 2.15 mg/kg DOX for 3 weeks, 7 doses in total (n=10). At the end of the experimental period, electrocardiogram (ECG) measurements were taken for all animals and evaluated.
Results: ECG data showed that heart rate (HR), P wave amplitude, and P duration did not differ between the acute and control groups but did statistically significantly declined in the chronic group. In both DOX groups, PR interval remained unchanged compared to the control. Also, RR interval increased significantly in the chronic group while it remained unchanged in the acute DOX dose group. The QRS duration was found to have considerably increased in both DOX groups. Furthermore, it was found that both DOX groups had a considerable increase in the QT interval, although the chronic group's increase was more noticeable.
Conclusions: In conclusion, it is thought that the ways in which these medications are administered may result in significant variations in heart function. Acute DOX treatment appears to be less harmful than chronic exposure, as evidenced by its lack of adverse effects, particularly on P wave amplitude (a measure of atrial contraction) and P wave duration (the length of the contraction). However, more research is required to validate these findings.

Key Words: Electrocardiogram (ECG), Doxorubicin (DOX), Cardiotoxicity

Öz

Amaç: Kanser tedavisinde kullanılan ilaçlar kalp sorunlarına neden olmakta ve bu da kullanımlarını kısıtlamaktadır. Ayrıca, bu ilaçların uygulanma yönteminin farklı sonuçlara neden olduğu görülmektedir. Bu nedenle bu çalışmada, doksorubisin'in (DOX) akut ve kronik olarak uygulanmasının kalbin elektriksel aktivitesi üzerinde farklı etkilerinin olup olmadığının incelenmesi amaçlandı.
Materyal ve Metod: Ağırlıkları 200-250 gram arasında değişen 26 adet erkek Wistar-Albino sıçan üç gruba ayrıldı: Kontrol grubu: hayvanlara herhangi bir tedavi uygulanmadı (n=8), DOX akut grubu; 3 haftanın sonunda 15,05 mg/kg DOX i.p. olarak verildi (n=10), DOX kronik grubu; 3 haftada yedi kez her defasında 2,15 mg/kg DOX intraperitoneal (i.p.) uygulandı (n=10). Deney süresi sonunda tüm hayvanlardan elektrokardiyogram (EKG) ölçümleri alınarak değerlendirildi.
Bulgular: EKG verilerine göre kalp atım hızı, P dalga genliği ve P süresinin akut ve kontrol grupları arasında farklılık göstermediğini ancak kronik grupta istatistiksel olarak anlamlı azaldığı görüldü. Her iki DOX grubunda da PR aralığı kontrole göre değişmedi. Ayrıca kronik grupta RR aralığı anlamlı derecede artarken akut DOX grubunda değişmedi. Her iki DOX grubunda da QRS süresinin oldukça arttığı görüldü. Ayrıca her iki DOX grubunda da QT aralığında ciddi bir artış olduğu ancak kronik grupta artışın daha belirgin olduğu görüldü.
Sonuç: Sonuç olarak bu ilaçların uygulanma şeklinin kalp fonksiyonlarında anlamlı değişikliklere yol açabileceği düşünülmektedir. Akut DOX tedavisi, özellikle P dalgası genliği (atriyal kasılmanın bir ölçüsü) ve P dalga süresi (kasılmanın uzunluğu) üzerinde olumsuz etkilerinin olmayışı ile, kronik maruziyetten daha az zararlı olabileceği düşünülmektedir. Ancak bu bulguları doğrulamak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Elektrokardiyogram (EKG), Doksorubisin (DOX), Kardiyotoksisite

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Introduction

Anthracycline antibiotic doxorubicin (DOX) is one of the most powerful and effective anticancer drugs on the market. It is used to treat a wide range of solid tumors, including ovarian, thyroid, and breast cancers, as well as hematological malignancies in humans (1). Nevertheless, due to the fact that DOX can cause a variety of cardiovascular disorders, including arrhythmia, irreversible cardiomyopathy, and congestive heart failure, depending on the cumulative dosage, its therapeutic usage is still restricted (1,2). Such heart conditions impair the body's defenses against harmful substances. The electrical and ionic state of the myocardium, particularly in relation to vasoactive chemicals and hormones, which are governed by the physiological state of the heart, determines how the cardiovascular system reacts to medications or hazardous compounds (3). Research has been conducted in both human and experimental animal models to demonstrate cardiac dysfunctions that restrict the use of DOX in cancer treatment (4,5). The generation of reactive free radicals and abnormalities in Ca^{2+} regulation are the primary causes of these cardiac diseases that arise with DOX treatment; arrhythmias and heart failure are known to follow (6). An essential tool for identifying potential heart problems is the ECG. Prior research has conducted ECG investigations on humans, which could demonstrate the harmful effects of exposure to hazardous agents like DOX (7,8). Similarly, the effects of these agents on the electrical activity of the heart in rodents, especially in rats, have been demonstrated by ECG measurements (9,10). However, it is noteworthy that studies showing the effects of acute and chronic application differences on ECG parameters are limited. This study sought to ascertain the effects of acute or chronic administration of the anti-neoplastic drug DOX on the ECG, which is a crucial marker of cardiac dysfunction, as well as the degree to which these various methods of application affect the different phases of the ECG signals.

Materials and Methods

Preparation of animals

Male Wistar-Albino rats weighing 200–250 g were used in the investigation. Three groups randomly assigned to: control group; no treatment was applied to animals (n=8), DOX acute group: a single dosage of 15.05 mg/kg of DOX was given to the at the end of the 3 weeks (n=8), DOX chronic group; which received an intraperitoneal (i.p.) dose of 2.15 mg/kg DOX seven times in 3 weeks (n=10). Doxorubicin was bought as Adrimisin® (50 mg/25 mL injectable solution) from Saba Pharmaceuticals (Istanbul, Turkey). A maximum of 3 animals were housed in each cage while the animals were maintained at 22 ± 2 °C room temperature. Additionally, the experimental procedure was carried out on animals with free access to food and water and 12-second light/dark cycles. The selection criteria included both an ethical minimum and an adequate number of animals for a statistically valid assessment. Akdeniz University Local Ethics Committee's guidelines for the use of animals in experimentation were strictly adhered to and approved with the decision numbered 2023/107 (Date: 09 November 2023, Protocol Number: 107).

ECG Recordings

Electrocardiographic measurements were taken at the end of the experiment. Intramuscular xylazine and ketamine doses of 10 mg/kg each were used to maintain the anesthetic state. The ECGs (lead II) of every animal were measured after a 3-minute anesthesia. ECG changes were recorded using the MP150 (Biopac Systems) equipment. All of the data were displayed as the frequently used ECG parameters: RR interval, HR, PR interval, P duration, QRS complex, QT interval, corrected QT interval (QTc), P amplitude, and R amplitude. The ECG values were analyzed using the Lab Chart program. Figure 1 shows the ECG recordings for each group.

Figure 1. The effect of acute or chronic DOX treatment on ECG traces (A: Control, B: Acute DOX, C: Chronic DOX).

Statistical analysis

For the statistical analysis, GraphPad Prism was utilized. The mean ± SEM is displayed for every experiment. To confirm normality and homogeneity, Shapiro-Wilk and Levene tests were utilized. To ascertain the difference between groups, all parameters were evaluated using a one-way ANOVA followed by a post hoc Dunnett test. *P* values less than 0.05 was considered to be significant.

Results

Figure 2 displays the electrocardiographic patterns (P wave amplitude, P wave duration, PR interval QRS complex duration, RR interval, QT interval, and QTc interval) that were obtained following the acute and chronic injection of DOX. HR is an expression that gives the number of heart contractions in a certain period of time. In line with the RR interval, it was shown that the chronic DOX treated group had a statistically significant decrease in HR (Fig. 2A). On the other hand, the results showed that P amplitude and P duration did not change in the acute DOX group, however, they showed a statistically significant decrease in the chronic DOX group (Fig. 2B, C). It was found that the PR interval in both DOX groups remained unchanged (Fig. 2D). While both the acute and chronic groups showed a substantial increase in the QRS complex, only the chronic group showed a significant increase in the RR interval compared to the control (Fig. 2E, F). Similarly, while though both DOX groups had a dramatic increase in QT interval, the increase in chronic administration seemed to be more noticeable (Fig. 2G). QTc was also significantly increased in both acute and chronic groups compared to the control (Fig. 2H).

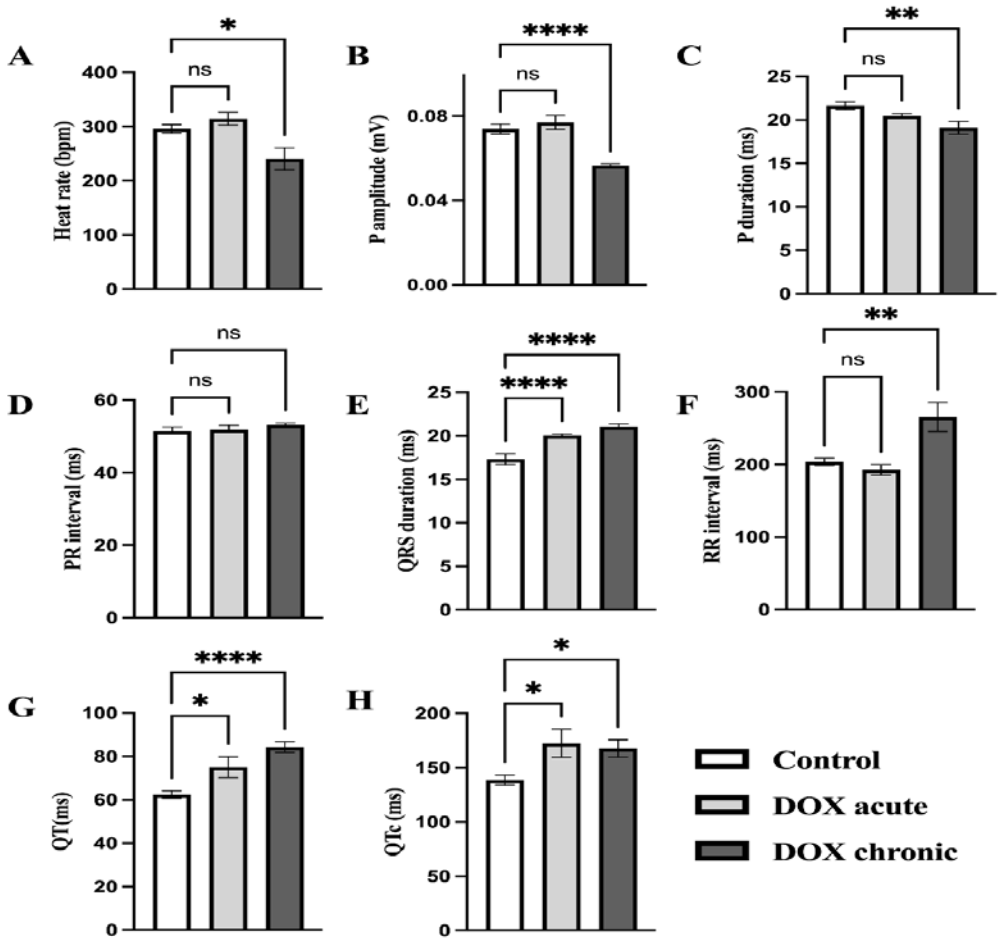

Figure 2. ECG evaluation of rats administered with acute or chronic doxorubicin. Each bar shows ECG-related parameters changes. Statistical comparison of means among all groups was performed using one-way ANOVA followed by Dunnett's test. *;p<0.05, **;p<0.01, ****; p<0.0001.

Discussion

One of the biggest concerns for oncologists is DOX-induced cardiac dysfunction, which restricts the use of DOX in clinical settings (11). The aim of this study is to evaluate the effects of a single acute dosage (15.05 mg/kg DOX) and a chronic treatment (2.15 mg/kg DOX for 3 weeks, 7 doses total) of DOX on cardiac function in rats using electrocardiographic measurements. The objective is to ascertain whether these two different application approaches differ from one another.

In order to identify cardiac dysfunctions or evaluate the electrical activity of the heart in patients receiving DOX therapy, ECG measurements are one of the essential clinical procedures (12). Notably, arrhythmias and conduction abnormalities are among the cardiac dysfunctions linked to acute DOX treatment (13,14). Conversely, chronic DOX treatments primarily cause an elongation of the QRS complex and QT interval. The former primarily leads in intraventricular conduction abnormalities and alterations in ventricular rhythm;

the latter produces hypokalemia, ischemia, myocardial infarction, and channelopathies (15,16). It has been demonstrated in numerous investigations that DOX significantly lengthens the QT interval, which is the first anomaly in the ECG that may be identified (17). In consistent with these results, the present investigation demonstrated that both acute and chronic administration of DOX resulted in a significant elevation of the QRS complex, also with the effects on the QT interval being most noticeable with chronic treatment. Furthermore, a prior investigation demonstrated that the administration of DOX results in an extension of the QT interval and is strongly associated with left ventricular dysfunction (17). It is commonly known that in humans, HR and the duration of the QT interval are closely correlated. Typically, a decrease in the HR value will result in a drop in the systole and diastole ratio, which causes an increase in the QT interval. QTc, which accounts for variations in HR, is frequently employed as a far more objective measure of the ventricles' depolarization and repolarization (18). The QTc interval was shown to rise statistically significantly in both the acute and chronic groups in this investigation, which is consistent with other research (14). Another major finding from this study was that that HR, P amplitude, P wave duration, and RR interval showed significant changes only in the chronic DOX applied group, and these parameters did not change in the acute DOX group. These reductions in P wave duration and amplitude are typically interpreted as a sign of atrial fibrillation (19). In general, HR is defined as the quantity of cardiac contractions in a minute. The time interval between two successive R peaks is known as the RR interval, and the RR interval time can be used to determine HR. The results of this investigation demonstrated a considerable increase in the RR interval and caused bradycardia because of low HR as a result of chronic DOX treatment. Acute DOX treatment was shown to have no effect on these parameters. While the majority of these findings align with earlier research, a few studies indicate that the use of DOX can induce tachycardia (20,21). Furthermore, a distinct study shown that giving 1.5 mg/kg and 3 mg/kg of DOX every time for three days resulted in significantly different outcomes for cardiac cells (22).

In light of the fact that ECG application is non-invasive, affordable, and simple to use, it can be a valuable tool in the early detection of DOX-induced cardiac dysfunctions. We used doxorubicin as a preparation in our study. We planned our research in this way because, in our literature review, no control group containing excipients was added to the studies in which doxorubicin was used as a preparation (23). In our future studies, we plan to investigate the main reasons for acute and chronic treatment differences. The results of this study also indicate that, though acute DOX treatment altered the QRS and QT interval, its effects on the heart's electrical activity appeared to be far less harmful than those of chronic exposure. Specifically, the lack of effect that acute application has on HR, P wave amplitude, and P wave duration raises the possibility that atrial dysfunction is not the cause. To ascertain whether the impacts on cancer cells result in a detrimental difference as compared to chronic treatment, the results obtained here need to be corroborated by other research and further investigations.

Ethical Approval: Akdeniz University Local Ethics Committee's guidelines for the use of animals in experimentation were strictly adhered to and approved with the decision numbered 2023/107 (Date: 09 November 2023, Protocol Number: 107).

Author Contributions:
Concept: Y.G., B.D., B.Ç.
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Design : Y.G., B.D.
Data acquisition: Y.G., B.D.
Analysis and interpretation: Y.G., B.Ç.,
Writing manuscript: Y.G., B.D., B.Ç.
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