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EFFECT OF PACLITAXEL ADMINISTRATION ON ELECTROCARDIOGRAPHIC PARAMETERS REFLECTING VENTRICULAR HETEROGENITY

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ÖZET: Son birkaç dekaddır tubulin dinamiklerini bozarak etki eden ve prototip bir taksan bileşiği olan paklitaxel, küçük hücreli olmayan akciğer kanseri, over ve meme kanseri, baş ve boyun kanserleri dahil olmak üzere birçok solid malignitenin tedavisinde yaygın olarak kullanılmaktadır. Ancak paklitaxel infüzyonu sırasında pekçok kardiyak yan etki rapor edilmiştir. Bu nedenle, bu çalışmada paklitaxel infüzyonunun elektrokardiyografi (EKG) üzerine etkisi araştırıldı. Çalışmaya meme (6 vaka), over (3 vaka) ve küçük hücreli olmayan akciğer kanseri (3 vaka) nedeniyle paklitaxel kemoterapisi alan toplam 12 hasta (7 kadın, 5 erkek ortalama 55±9 yaş) alındı. Tüm hastalarda paklitaxel infüzyonundan hemen önce ve infüzyondan 1 saat sonra EKG kaydedildi. Tüm kayıtlar 12 derivasyonlu yüzey elektrokardiyogramında alındı. Ventriküler heterojeniteyi gösteren elektrokardiyografik parametreler manuel olarak hesaplandı. Ortalama kalp hızı, maksimum QT, düzeltilmiş QT ve QRS interval süresi infüzyon sonrası değişmedi. (Ortalama kalp hızı; 85±5 ve 79±4 atım/dakika, maksimum QT 414±22 ve 420±24 ms, QTc 412±25 424±15 ms, ortalama QRS interval süresi 93±4 ve 95±5 ms p>0.005). Ancak düzeltilmiş QT dispersiyonu infüzyon sonrası belirgin olarak arttı (düzeltilmiş QT dispersiyonu 41±9 ve 70±11 ms p< 0.005). Sonuç olarak paklitaxel infüzyonu sonrası artmış QT dispersiyonu, otonomik disfonksiyonu yansıtır ve aynı zamanda bu ilaçtan kaynaklanan ciddi potansiyel aritmi riskini de gösterebilir. Ancak, paklitaxel infüzyonuna bağlı kardiyak yan etkilerin altta yatan mekanizmasını aydınlatmak için daha fazla çalışmaya ihtiyaç vardır.
[Anahtar kelimeler: QT dispersiyonu, paklitaxel, aritmi]

ABSTRACT: During past several decades the prototypic taxane paclitaxel, which disrupt tubulin dynamics, has been widely used in treatment of solide malignancies, including non-small cell lung carcinoma, ovarian and breast, head and neck cancer. However, a variety of cardiac adverse effects have been reported during paclitaxel therapy. Therefore, in this study effect of the paclitaxel infusion on electrocardiogram was investigated. Twelve patients (7 female, 5 male mean 55±9 years) receiving paclitaxel chemotherapy because of breast (in 6 cases), ovarian (in 3 cases), non-small cell lung (in 3 cases) carsinomas were included to study. For all patients just before infusion and 1 hour after the end of infusion electrocardiogram were recorded. All records were obtained on a routine 12 lead surface electrocardiogram. Electrocardiographic parameters suggesting ventricular heterogeneity were calculated manually. Mean heart rate, QT max, corrected QT (QTc) and QRS interval duration did not change after infusion. (Mean heart rate; 85±5 vs. 79±4 beats/min., QT max. 414±22 vs. 420±24 ms, QTc 412±25 424±15 ms, mean QRS interval duration 93±4 vs. 95±5 ms p>0.005). However, corrected QT dispersion (QTcd) significantly increased after infusion (QTcd 41±9 vs. 70±11 ms p< 0.005). In conclusion, increased QT dispersion after paclitaxel infusion reflects autonomic dysfunction and it may also suggest the risk of potential serious arrhythmias arising from this drug. However further studies are warranted to elucidate the underlying mechanism of cardiac adverse effects relevant to paclitaxel.
[Key words: QT dispersion, paclitaxel, arrhythmia]

INTRODUCTION

Paclitaxel, an antimicrotubule agent that disrupts tubulin dynamics, has been used in treatment of many common types of solid malignancies including methastatic breast carcinoma, advanced ovarian carcinoma and non-small cell lung carcinomas (1-3). Cardiac side effects including ventricular tachycardia, atrial arrhythmias, ischemic events and sudden death have been reported associated with paclitaxel therapy (4,5). However, the factors that increase the risk for cardiotoxicity, and rhythm disturbances have not been identified in patients receiving paclitaxel. Measurement of the variability in QT interval duration among the 12- leads of the standard electrocardiogram (ECG), called QT dispersion, has been proposed as a practical method for the evaluation of the nonhomogenity of ventricular recovery time (6). Therefore, this study was designed to test whether the paclitaxel therapy increases in susceptibility to ventricular arrhythmias.

MATERIALS AND METHODS

Twelve patients (7 female, 5 male, mean 55±9 years) receiving paclitaxel chemotheraphy because of breast (in 6 cases), ovarian (in 3 cases) and non-small-cell lung (in 3 cases), carsinomas were included to study. For all members paclitaxel was the single therapeutic agent and study was done during first course of therapy. No one had previous received chemotherapy. Three of 12 patients had the history of prior radiotherapy and two of them had priorly experienced surgical intervention. Before administration of paclitaxel, a history was taken and complete physical examination was performed and complete blood count, routine biochemical and electrolyte profiles, urine analysis, chest radiograph and electrocardiogram was obtained. Blood sample was taken to exclude electrolyte abnormalities that could be affect on electrocardiogram (ECG). Paclitaxel was infused at a dose of 175-200 mg/m^2 over one hour with recommended antihistamine premedication.

Just before the first course of therapy and 1 h after the end of infusion ECG was recorded. Before and after infusion echocardiographic evaluation was done. Patients with cardiac disease and those on medications known to alter cardiac conduction were excluded from the study. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. QT dispersion, defined as the maximum minus minimum QT intervals, and corrected QT (QTc) was measured according to Bazett's formula to adjust heart rate. (7) QT maximum and QT dispersion were measured in all leads of a 12-lead ECG recorded at a speed of 50 mm/s for 2 consecutive cycles. None of the 12 study subjects had a U wave superimposed on the terminal portion of the T wave. If the T wave could not be reliably determined or if it had very low amplitude, QT measurements were not obtained and these leads were excluded from the analysis. Two independent experienced observers who were unaware of the clinical details examined QT dispersion measurements. The third observer verified disagreement between observers.

STATISTICAL ANALYSIS

Data are expressed as the mean values. Comparison of date was performed with the Student t test and for comparison of QT interval before and after infusion Mann Whitney U test was used. A p-value <0.05 was considered to indicate statistical significance.

RESULTS

All patients well tolerated the therapy. During administration was not seen any rhythm disturbances including ventricular tachyarrhythmias, conduction defects, S-T segment changes and hemodynamic change. Before and after administration hemodynamic change and electrolyte abnormalities were not detected (Table-I). ECG parameters are listed

in Table-II. During echocardiographic analysis valvular disorders, left ventricular hypertrophy and wall motion abnormalities and clinically significant valvular regurgitation were not detected. All members had sinus rhythm. There was no any record with low-amplitude and with U waves. The number of the leads in which QT intervals could be measured was similar before and after infusion (range 8 to 12). There was no statistical differences with regard to mean heart rate before and after infusion (Mean heart rate; 85±5 vs. 79±4 p>0.005). Mean QRS interval durations, QTmax, and corrected QT (QTc) did not change after infusion (mean QRS interval duration 93±4 vs. 95±5 ms, QTmax. 414±22 vs. 420±24, and QTc: 412±25 vs. 424±15 p>0.05). However, corrected QT dispersion (QTcd) significantly increased after infusion. (QTcd 41±9 vs. 70±11 p< 0.005). There was no association between the dose of paclitaxel and QTd, QTcd.

Table-I: Hemodynamic and biochemical values

Variable	Before infusion	After infusion
Mean blood pressure (mmHg)	87 ±7	84 ± 5
Blood glucose level (g/dl)	80 ±6	82 ± 5
Na (mmol/L)	140 ±4	139 ± 4
K^+ (mmol/L)	4.4 ± 0.2	4.4 ± 0.3
Ca^{++} (mmol/L)	9.3 ± 0.3	9.4 ± 0.2
Cl (mmol/L)	105 ± 0.9	104 ± 1.0
Ejection Fraction (%)	64 ±5	63 ± 4

Table-II: Comparison of ECG parameters

Variable	Before infusion	After infusion
Mean Heart Rate (beat/min)	85 ± 5	79 ± 4
Mean QRS duration, ms	93 ± 4	95 ± 5
QTmax	414 ± 22	420 ± 24
QTc, ms	412 ± 25	424 ± 15
QTcd*, ms	41 ± 9	70 ± 11

* p< 0.005 Statistically significant

DISCUSSION

In the present study we found that administration of the paclitaxel increased QTc dispersion. It is known that increased QTcd is associated with increased susceptibility to ventricular arrhythmias and reflects the regional variation in ventricular repolarization, which may increase the risk of sudden death caused by malignant arrhythmias (8,9). Although cardiac rhythm disturbances have been widely observed during paclitaxel therapy, their importance and exact mechanism are not known. Until today, no previous studies have examined electrocardiographic changes observed in patients receiving paclitaxel and their relation to susceptibility to arrhythmias. Thus, our study is the first showing increased QTcd during paclitaxel infusion. From this point of view, we hypothesized that paclitaxel exhibits increased ventricular susceptibility,

even during asymptomatic phase and this may predispose the patient receiving paclitaxel therapy to the development of malignant ventricular arrhythmias. Since QT dispersion reflects ventricular heterogeneity, it may provide important clinical benefits, particularly in the assessment the risk of arrhytmogenic drug. The prolonged QT interval is regarded as a marker of imbalanced distribition of sympathetic nervous system activity on the heart, indicating that the autonomic neural tone is an important determinant of QT interval duration and dispersion (10-12). Previous studies have shown that QT dispersion is abnormally increased in patients with primary autonomic failure (10). It has also been shown that important infuence of autonomic nervous systems on QT interval in diabetic patients with autonomic neuropathy (12) in cardiac transplant recipients with autonomically denervated hearts (13) and by using pharmacologic agents that block either limb of autonomic nervous system (14). Several cardiac side effects such as mobitz types I (Wenckebach syndrome), II and third-degree heart block, myocardial ischemia, myocardial infarction, atrial arrhythmias and ventricular tachycardia have been noted during paclitaxel therapy (4,5,16). Furthermore, cardiac death resulting from paclitaxel therapy has been reported (15). Our finding with increased QT dispersion suggest that paclitaxel may predispose the patients to arrhythmic event and may increases the risk of sudden death. It is likely that rhythm disturbances caused by paclitaxel are related cardiac automaticity and conduction changes. This hypothesis has been supported by some clues, for example, similar disturbances have occurred in humans and animals after the ingestion of yew plants which are the basic substances of paclitaxel (16). Thus, we attributed the increase in QT duration to impaired cardiac autonomia after paclitaxel infusion. Previously, Ekholm et al. (17) reported that paclitaxel changes sympathetic control of blood pressure examined with a battery of autonomic function tests. Ekholm et al. (18) also reported reduced low frequency/high frequency ratio and attenuated circadian rhyhm of heart rate variability and claimed that autonomic cardiac modulation is impaired after the course of paclitaxel. Our findings are in accordance with the hypothesis that autonomic cardiac modulation is impaired during paclitaxel therapy as reported by Ekholm et al (18). On the other hand, it has been reported that paclitaxel induces motor and autonomic dysfunction especially at high doses and in patients with preexisting neuropathies caused by diabetes mellitus and alcoholism (19). These findings suggest that paclitaxel not only impair cardiac autonomy but also effects peripheric and santral autonomic function. If the measurement errors and poor reproducibility of QTc dispersion method are given, reported risk estimates are likely to be substantially diluted. However, we believe that this simple and cheap method is a strong and independent predictor of ventricular heterogenity and cardiac mortality. Hence, it can be easily used to estimate arrhythmia risk during paclitaxel administration. In conclusion, increased QT dispersion after paclitaxel infusion reflects that cardiac autonomic modulation is impaired and it may also suggest the risk of potential serious arrhythmias arising from this drug. However further studies are warranted to elucidate the underlying mechanism of cardiac adverse effects relevant to paclitaxel.

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