

The prevalence of silent arrhythmia in patients receiving cisplatin-based chemotherapy

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ABSTRACT

Cisplatin has been used effectively in oncology practice for a long time. No sufficient clinical evidence exists about the arrhythmogenic potential of this drug. The purpose of this study is to determine the frequency, types and clinical significance of the arrhythmias that occur during or shortly after treatment in patients receiving cisplatin-based chemotherapy. Thirty patients with malignant diseases who were indicated to receive chemotherapy regimens including cisplatin were prospectively enrolled into this study. Electrocardiographic and echocardiographic assessments of the patients were performed before and immediately after cisplatin infusion. QT dispersion values were calculated from electrocardiographic records. Serum electrolyte levels, blood pressure and heart rate values were determined before and after treatment as well. Holter monitoring of 24 hour was performed on the first day following chemotherapy. Comparison of heart rate, blood pressure, serum electrolyte levels, electrocardiographic and echocardiographic parameters before and after cisplatin infusion revealed only significant difference in QT dispersion values. According to the analysis of Holter records, asymptomatic silent arrhythmias were detected in 20 patients (66.7%). The mechanism of cisplatin-induced silent cardiac arrhythmias seems to be independent of changes in the serum electrolyte levels. Cisplatin induced arrhythmias may be due to the direct effect of the drug on cardiac sodium channels which leads to an increase in QT dispersion. [Turk J Cancer 2008;38(1):12-15]

KEY WORDS:

Arrhythmia, cisplatin, cardiotoxicity

INTRODUCTION

Chemotherapy may induce entire spectrum of cardiac pathology. Although cisplatin has been used in therapy of common cancers, there is no sufficient clinical evidence regarding the cardiotoxicity of this drug. There are few case reports of arrhythmia including supraventricular tachycardia, bradycardia and conduction abnormalities caused by cisplatin infusion in the literature (1-6). Majority of these cardiac problems were reported to be clinically silent. Although published studies showed that cisplatin induced arrhythmia was unrelated to electrolyte imbalance there is not enough data about prevalence and mechanisms of arrhythmias caused by this commonly used drug (7,8).

In this cross-sectional study, we aimed to determine the frequency, types and clinical significance of arrhythmia which could occur during or shortly after drug administration in patients receiving cisplatin-based chemotherapy.

PATIENTS AND METHODS

Thirty patients with malignant diseases in whom cisplatin-based chemotherapy was indicated, were prospec-

tively enrolled into the study. The patients younger than 18 and older than 70 were not included. Patients with cardiac involvement by tumor, acute coronary syndrome, severe arrhythmia and heart failure were excluded. Those who were on any medication or patients with pacemaker which could affect QT interval were not involved.

Patients received different cisplatin based chemotherapy regimen considering their underlying malignancy. Cisplatin was given on the first day of the treatment.

Before treatment, each patient was questioned about present symptoms or past history of cardiovascular disease as well as medications which might affect the QT interval and physical examination was performed. Serum electrolyte levels (potassium, sodium, calcium, magnesium) were measured. Blood pressure and heart rate estimations were noted. Electrocardiographs (ECG) of the patients were recorded before cisplatin, and echocardiographic assessments including calculations of diameter of left ventricular in systole and diastole, and ejection fraction were also done.

Immediately after cisplatin infusion, patients were physically re-examined and biochemical assessments were performed again. ECG and echocardiographic assessments were retaken.

For each patient, Holter records were obtained for 24 hour with a Dynacord model 419 instrument on the day which infusion of cisplatin was performed. Del Mar Avionics model 500 equipment was used for data analysis.

Presence of supraventricular arrhythmia was categorized as follows:

- 0: no supraventricular arrhythmia;
- 1A: <30 supraventricular premature beats/hour;
- 1B: > 30 supraventricular premature beats/hour;
- 2: supraventricular couplets;
- 3: ≥ 1 episode of supraventricular tachycardia;
- 4: flutter or atrial fibrillation.

The presence of ventricular arrhythmia was categorized according to Lown classification:

- 0: no ventricular arrhythmia;
- 1: <30 ventricular premature beats/hour;
- 2: >30 ventricular premature beats/hour;
- 3: multiform ventricular premature beats;
- 4A: ventricular couplets;
- 4B: three or more consecutive ventricular premature beats.

QT intervals, defined as the interval from the beginning of the QRS complex to the end of the T wave, were measured manually with the help of calipers in all 12 leads by a single observer who was blinded to the study. The QTc, QT interval corrected for the heart rate, was calculated from The ECG by Bazett's formula QT/\sqrt{RR} and expressed in milliseconds. The measures of the dispersion for QT and QTc intervals (QTd and QTcd), the differences between the maximum and minimum QT and QTc intervals, respectively, were also performed.

Statistical analysis

All statistical studies were carried out with SPSS program (version 10.0, SPSS, Chicago, Illinois, USA). All data are presented as mean \pm SEM. Measurements before and after cisplatin therapy were analyzed using Paired-samples t test or Wilcoxon test where appropriate. A p value of less than 0.05 was used to infer statistical significance.

RESULTS

The mean age of patients enrolled in to the study was 46.93 (18-69). Seven (23.3%) and 23 (76.7%) patients were female and male, respectively. Most of the patients had lung cancer in advanced stage. Distribution of the patients according to the underlying malignancy and stage of the disease is shown in table 1.

The most commonly used chemotherapy regimen was the combination of cisplatin and etoposide. The median of daily cisplatin dose was 51.5 mg/m² (20-100 mg/m²) given in range of 1-5 cycles of chemotherapy.

Before the cisplatin infusion, no abnormality was observed considering physical examination, ECG records, echocardiographic assessments, and serum electrolyte measurements. Thyroid function tests were also in normal ranges.

Holter analysis demonstrated supraventricular or ventricular arrhythmia in any degree (1-4) was detected in 20 patients (66.7%) all of whom were asymptomatic during the arrhythmia attacks. The arrhythmias were atrial, ventricular and both atrial and ventricular in origin in 3, 7 and 10 patients, respectively. No conduction disturbance was recorded.

Table 1
The distribution of the study group according to underlying malignancy and stage of the disease

Disease	Stage			Total
	I	II	IV	
Lung cancer	-	-	14	14
Head and neck cancer	1	4	2	7
Gastric cancer	-	-	2	2
Breast cancer	-	-	1	1
Malignant melanoma	-	-	1	1
Sarcoma	-	-	2	2
Germ cell tumor	-	1	1	2
Hodgkin's disease	-	1	-	1
Total	1	6	23	30

Table 2
Distribution of systolic and diastolic blood pressure, pulse rate and QT dispersion values of patients before and after cisplatin infusion*

	Before cisplatin	After cisplatin	P
SBP (mmHg)	123.3±1.75 (110-140)	122.3±1.49 (110-140)	0.37
DBP (mmHg)	79.3±0.17 (70-90)	80.0±0.68 (70-90)	0.60
Pulse (beats/min)	80.3±1.78 (60-112)	81.7±2.01 (66-122)	0.53
QT dispersion (milisec)	47.3±5.47 (0-120)	63.3±6.22 (0-120)	0.01

* Values are expressed as mean±SEM (min-max)

SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Analysis of parameters of 30 patients before and after cisplatin infusion including heart rate, blood pressure, serum electrolyte levels, echocardiographic parameters and QT dispersion, revealed only significant difference ($p < 0.01$) in QT dispersion values. Distribution of these parameters are given in table 2.

DISCUSSION

In this study, the prevalence of cisplatin-related acute arrhythmia in any degree was found as 66.7%, all of which were silent. Although, there is no data in literature about prevalence of arrhythmia induced by cisplatin based chemotherapy, this prevalence encountered in our study group seems to be higher than expected.

Also, there is not enough data about the pathogenesis of arrhythmia caused by cisplatin infusion. Entire spec-

trum of arrhythmia, including supraventricular tachycardia, bradycardia and block in any degree may be observed during or shortly after cisplatin administration, some of them being clinically important and may cause death (1-6). Arrhythmias caused by anticancer drugs may occur during and shortly after drug administration by different possible mechanisms such as direct effects of drug on heart (doxorubicin, daunorubicin, cisplatin, paclitaxel), coronary artery spasm (5-fluorouracil, bleomycin, paclitaxel), electrolyte imbalance (amsacrin, alpha-interferon, IL-1, IL-2, IL-11) and autonomic cardioneuropathy (vincristine, irinotecan). There is no known toxic effect of cisplatin on myocardial cells directly, but a possible side effect on coronary arteries has been reported (6). But ECG records of patients taken during cisplatin infusion may reveal signs of acute ischemia and also symptoms and signs

of acute coronary vascular disease could be observed during cisplatin infusion (9). The other possible mechanisms for cisplatin related arrhythmias include electrolyte imbalance that might occur after cisplatin administration.

In this study, to elucidate the possible mechanisms of arrhythmias caused by cisplatin; vital signs, serum electrolyte levels, echocardiographic and electrocardiographic signs were compared before and after the drug administration. No change was observed in sodium, potassium, magnesium, calcium levels before and after drug administration revealed no difference.

QT dispersion defined as the interlead variability of the QT interval, is an electrocardiographic marker of differences in ventricular repolarization. During the past decade, numerous publications have reported physiological and/or clinical value of QT dispersion measurement. Increased QT dispersion has been reported to be associated with increased risk of ventricular arrhythmias and sudden death (10-13).

QT dispersion before and after cisplatin revealed sig-

nificant difference in all patients including those with arrhythmias. Increasing QT dispersion may be possible explanation for cisplatin-induced arrhythmias. In Brugada syndrome and congenital form of long QT syndrome which are characterized as increase in QT dispersion and lethal arrhythmias, mutations were shown in genes regulating phase I of action potential of sodium channels. Blockage of these channels cause disturbance in homogeneity of ventricular recovery time and re-entry (10,11,15). In addition, some medications such as tricyclic antidepressants, phenothiazines and antihistaminics and electrolyte imbalance may cause increase in QT dispersion also by affecting these channels (12-16).

It might be concluded that the mechanism of cisplatin-induced cardiac arrhythmias seems to be independent of changes in the serum electrolyte levels and may be due to the direct effect of the drug on cardiac sodium channels leading to an increase in QT dispersion or any other mechanism which may cause in homogeneity of ventricular recovery.

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