The effects of zoledronic acid on ECG: a prospective study on patients with bone metastatic cancer

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Summary

***Introduction*. There are controversial results in the risk of atrial fibrillation as well as arrhythmogenic potential of bisphosphonates.**
***Method*. 37 patients and 40 healthy controls were evaluated prospectively with regard to the cardiac side effects related to the use of zoledronic acid (ZA) and its effects on electrocardiography (ECG) parameters.**
***Result*. As the basal ECG results of the patients diagnosed with cancer compared with the control group, it was determined that QT maximum was significantly lower, QT minimum was significantly higher. However; it was determined that QT disp, P max, P min, and P disp values were not significantly different. There was no statistically significant difference in P max, P min, P disp, QT max, QT min, QT disp values of the ECG parameters measured from cancer patients, before and 60 minutes after ZA therapy.**
***Conclusion*. There were no significant alterations in ECG in the acute period, indicated that ZA had no arrhythmia potential in the early period in patients with no underlying cardiac disease. However: patients receiving ZA should be monitored more closely because of the risk of arrhythmia which may ensue due to hypocalcemia, hypomagnesemia, or other chemotherapeutics.**

KEY WORDS: zoledronic acid; ECG; arrhythmia.

Introduction

Bisphosphonates are agents inhibiting bone resorption *in vitro* and *in vivo* and they have been demonstrated to have effects on hypercalcemia secondary to malignancy in cancer patients. Furthermore, they have effects on delaying or obviating the cancer-related skeletal system morbidity, bone pain, pathological fractures, and the necessity for radiotherapy (1). Zoledronic acid (ZA) is a third-generation bisphosphonate containing heterocyclic nitrogen with imidazole side-chain ring. The difference from the other bisphosphonates is the presence of second nitrogen atom in the ring structure (2). The most common side effects of ZA therapy in cancer patients with bone metastasis are fatigue, anemia, myalgia, fever and swelling in the legs, renal failure, and hypocalcemia. Jaw necrosis is a rare side effect in patients with multiple myelomas treated with ZA (2, 3). The cardiovascular side effects are: atrial fibrillation (AF), bradycardia and hypertension or hypotension. In HORIZON-PFT study, which is performed included 3900 patients, it was demonstrated that the risk of AF has increased twofold in patients treated with ZA in comparison to the normal population (4). In a study by Black et al. included 7700 patients, and that by Cummings et al. in 6500 patients, it was determined that the therapy with ZA and alendronate increased the risk of AF; however, there was no significant increase in cardiovascular mortality and stroke risk (5). Although there are controversial results in the risk of AF; the arrhythmogenic potential and ECG findings of ZA is not known definitely. In this context, for the first time we researched early ECG findings in cancer patients with bone metastasis treated with ZA.

Method

In this study, 37 patients were evaluated prospectively with regard to the cardiac side effects related to the use of ZA and its effects on ECG parameters. The study was conducted in oncology clinic of Bulent Ecevit University Medical Faculty Hospital between May 2011 and April 2012. Oral and written consents were obtained from all the patients.
Our inclusion criteria for the study are having cancer diagnosis and newly diagnosis of bone metastasis. Exclusion criterias were: malign hypercalcemia required acute dialyses, determination of hyperpotassemia, previous use of antiarrhythmic drug and antihypertensive drug, the presence of uncontrolled diabetes mellitus and the presence of history of ischemic heart disease.

ECG Measurement

Standard 12-lead ECG recordings were used in measurements. ECG recordings were performed just before ZA administration. The measurements were repeated 60 minutes after ZA administration. ECG recordings were taken at the rate of 25 mm/s. The ECG recordings which were obtained were transferred to a computer as image files with a resolution of 200 ppi (by JPG extension) through the scanner. QT and RR intervals of saved image ECG files recordings in 12-leads were measured by using Adobe Photoshop CS4 soft-

ware. Corrected QT interval (QTc) was calculated by using Bazzett formula (QTc = QT/√RR).
The subtraction of the longest corrected QT interval (QTc max) from the shortest corrected QT interval (QTc min) received from all leads was deemed as QT dispersion (QTd= QTc max-QTc min).
Statical analyses: Descriptive and basic data were identified as mean and standard deviation in those presenting normal distribution and as median and low-high range in those not presenting normal distribution. In group comparisons, Student's t-test was used as the parametric test and non-parametric Mann-Whitney U test was used according to the data distribution. The values before and after treatment were calculated by Paired Sample test. All P values were calculated bi-directionally. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used in statistical calculations. The results were evaluated in the confidence interval of 95% and the significance level of p<0.05.

Results

There were 21 females and 16 males in the test group, whereas there were 24 females and 16 males in the control group. 14 patients had breast cancer, 8 patients had colorectal cancer, 4 patients had lung cancer, 4 patients had gastric cancer, 5 patients had prostate cancer, 1 patient had renal cancer and 1 cancer had ovarian cancer. Ten patients had other organ metastases with concomitant bone metastasis. The locations of metastases except for bone were respectively: liver in 5 patients, lung in 3 patients, ovarian in 1 patient and soft tissue in 1 patient. The mean age of the patients were 48,9 ±16,3, ranging from 26 to 80 years.
As the general characteristics of both groups were compared, the biochemical parameters seen in patients diagnosed with cancer were AST (35,78), ALT (29,51), Ca (9,70), WBC (7216,22) and creatinine (0,95). As compared to control group, serum AST (35 *vs* 23 u/l, p=0.02), ALT (29 *vs* 20 u/l, p=0,01), Ca (9,7 *vs* 9,1 mg/dl, p=0,003), WBC (7216 *vs* 7077 K/Ul, p=0,002) and creatinine (0,9 *vs* 0,7 mg/dl, p=0,04) levels were found higher. However, PLT (235,03-253,40, p=0,006) value was significantly lower in patients diagnosed as cancer. In contrast, no statistically significant difference was detected in Hb values (Table 1).
As the basal ECG results of the patients diagnosed with cancer compared with the control group, it was determined that QT maximum was significantly lower (0,44 *vs* 0,32, p=0,0001), QT minimum was significantly higher (0,34 *vs* 0,42, p=0,004) (Table 2). However, it was determined that QT disp, P max, P min, and P disp values were not significantly different.
There was no statistically significant difference in P max, P min, P disp, QT max, QT min, QT disp values of the ECG parameters measured from cancer patients, before and 60 minutes after ZA therapy (Table 3).

Discussion

In our study researching early arrhythmia potential of ZA infusion in 37 cancer patients with bone metastasis and a control group of 40 patients, no significant alteration was ob-

Table 1 - Comparison of general characteristics.

Parameter	Patient Group (n: 37)	Control Group (n:40)	p Value
Age (age±SD)	53.70±14.1	44.63± 17.22	0.860
Hb (g/dl±SD)	11.33±1.53	13.13± 1.31	0.260
AST (U/l±SD)	35.78±17	23.93±9.23	0.020
ALT (U/l±SD)	29.51± 14.1	20.43± 9.2	0.010
Ca (mg/dl±SD)	9.70±0.77	9.12±0.47	0.003
Platelets (1000/µl±SD)	235.03±109.72	253.40±55.68	0.006
Leukocyte (1000/µl±SD)	7.21± 3.34	7.08±1.72	0.002
Creatinine (mg/dl±SD)	0.95± 0.23	0.71±0.15	0.040

(p <0.05, statistically significant)
Hb: Hemoglobin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, Ca: Calcium, PLT: Platelets, WBC: Leukocyte.

Table 2 - Comparison of basal ECG results of both groups.

Parameter	Group 1 (n: 37)	Group 2 (n: 40)	p value
P min	0.04±0.01	0.05±0.01	0.800
P max	0.01± 0.02	0.10±0.01	0.130
P Disp	0.05±0.01	0.04±0.02	0.760
QT min	0.34±0.06	0.42±0.04	0.004
QT max	0.44± 0.06	0.32± 0.04	<0.001
QT Disp	0.1±0.02	0.1±0.02	0.800

Table 3 - ECG Characteristics of Cancer Patients before and 60 minutes after ZA Therapy.

Parameter	ECG taken before treatment	ECG taken 1 hour after treatment	p value
P min	0.05±0.02	0.05±0.02	0.760
P max	0.10±0.02	0.10±0.02	0.480
P disp	0.05±0.02	0.05±0.02	0.200
QT min	0.34± 0.06	0.34± 0.06	0.740
QT max	0.45±0.06	0.45±0.07	0.420
QT disp	0.11±0.02	0.11±0.03	0.570

served in QT disp, P disp and the other rhythm findings in ECG of cancer patients with bone metastasis by ZA infusion. By this evidence, it was revealed that ZA had no negative arrhythmogenic effects in the acute period in patients treated with this drug. It was considered why the liver function tests were significantly higher, and PLT values were significantly lower, and serum creatinine and calcium levels were insignificantly higher in cancer patients with bone metastasis as compared to control group were likely dependent to systemic involvement of cancer and its metastases. It was also demonstrated in our study that these findings do not provide an additional contribution to the risk of arrhythmia clinically.

An increase in P wave dispersion is accepted as an independent risk factor for atrial fibrillation regardless of the presence of overt heart disease (6). A significant correlation between increased P wave dispersion and atrial fibrillation is demonstrated in patients with hypertension, dialysis, coronary by-pass history, COPD, hyperthyroidism and hypothyroidism (6-9). In most of these researches, the increased P dispersion was dependent on increase in P max duration. Also QT dispersion is accepted as a risk factor for ventricular arrhythmia (10). Especially in those with QT dispersion >100ms, it was found to be a risk for serious ventricular arrhythmia (10). In Rotterdam study, more than 6000 adults were analysed and when all the other known risk factors were equalized, it was demonstrated that the increased QT dispersion elicited an increase in cardiac mortality (11). We analyzed these parameters in ECG in patients treated with ZA before drug and 60 minutes after drug, because they are accepted as good indicators and predictive markers of atrial and ventricular arrhythmias.

Atrial fibrillation is the most frequent cardiac arrhythmia and this frequency is 1% under 60 years old, and it reaches 9% in the age of 80 years (12). AF is frequently correlated with hypertension, heart failure, myocardial ischemia, mitral stenosis, thyrotoxicosis, excessive alcohol consumption and cardiac surgery so we excluded patients with these diseases in our study. Bisphosphonates are particularly used in osteoporosis treatment, in cancer patients with bone metastasis, and in Paget's disease (13). Approximately 30 million oral bisphosphonates have been prescribed in USA. In recent years at some observational studies, it was demonstrated that bisphosphonates, which have been prescribed very frequently, elicited an increase in the risk of cardiac arrhythmias, especially in AF. First of these studies is HORIZON study; about 7800 patients diagnosed with postmenopausal osteoporosis were initiated ZA and after three-years follow-up, a significant decrease was observed in the risk of vertebral and non-vertebral fracture (14). However, a significant increase in the risk of arrhythmia was spotted by comparison to the placebo group in this study (6.9 *vs* 5.3%, P=0.003). Also, among the serious side effects, the number of the patients diagnosed with AF, which is fatal and requiring hospitalization or causing an increase in morbidity, was higher in the set of ZA (50 *vs* 30 patients, P=0.001). In this study, in 47 of 50 patients resulting serious side effects, the symptoms occurred 30 days after ZA infusion. However, the arrhythmogenic findings (P disp and QT disp) were not monitored in ECG. In another study (FIT study), published after HORIZON, oral alendronate administration was compared to placebo included 6500 postmenopausal female, and AF frequency was detected in 47 (1.5%) *vs* 31 (1%) (15).

In the randomized double-blind analyses performed subsequent to these studies, conflicting results were revealed. In one study, ZA infusion administration and placebo was compared in 1100 patients with previously observed fracture, there were similar arrhythmia and AF frequencies spotted in both groups (2.8 *vs* 2.6%, P>0.5) (16). In a phase-3 study, about 15,000 postmenopausal females who use risedronate compared to placebo and there were no significant increase determined in the risk of AF (17). In an observational study, conducted in Denmark, about 13,500 females diagnosed with AF or atrial flutter were compared to a control group of 68000 patients and in both groups, there were no significant differences in terms of bisphosphonate use and also only 3.2% of these patients diagnosed with AF (435 patients) were treated with bisphosphonate (18). However, in a broader survey performed in the same community, 15,795 patients with AF and using bisphosphonate compared to a control group of 31590 patients were investigated (19). An increase of 1.29 fold was found in the risk of AF (CI 1.17-1.41). Nevertheless, this significant value was decreased after excluding the other co-morbid conditions, bisphosphonates which are used in case of underlying cardiac problems may trigger AF is suggested by researchers. In a data survey of FDA in USA, about 20,000 patients treated with bisphosphonate and a control group of 19,000 patients receiving placebo were compared and between both groups there were no significant differences in the risk of AF by the end of the sixth month and third year and the risk of AF was found to be quite low, such as 0.3% (20). In an analogous study which was conducted in England, no significant correlation were found between the risk of AF and the use of bisphosphonate (21). In a study, pamidronate and ZA administration have been compared on patients with multiple myeloma and breast cancer in the terms of cardiac side effects. There was no placebo group in this study, and there was more frequent AF was detected in the set of PA *vs* ZA (2.2 *vs* 0.5%, P=0.18) (22). In the former of two meta-analysis on this topic, there was a significant increase seen in the risk of AF re-

sulting in serious events (odd ratio 1.47, P=0.04), while there was no significant increase in the frequency of AF which was not resulting in serious complications (P=0.15) (23). In another meta-analysis, Mak et al. indicated that there was a linear relationship between the use of bisphosphonate and AF (24). Most of the data derived from these studies are composed of drug safety monitoring. Also, the term "AF resulting in serious events" may vary according to researchers and may elicit discrepancies in interpretation and conclusion. As a matter of fact in some studies there was a risk of AF close to 4% whereas in some studies this ratio was found to be 0.3%, so this point supports our view. Besides, in studies in the literature, they have been suspicious of AF clinically, and paroxysmal AF's have been underdiagnosed due to the fact that there were no regular ECG recordings. Also, in none of the studies with ECG recordings, arrhythmogenic factors in ECG (QT disp, P disp, etc.) have not been monitored or reported. In this sense, our study is the first one in the literature. On the other hand, the great majority of the studies have been conducted in non-cancer patients (osteoporosis).

In a study performed in our community, Yazici et al. investigated cardiac arrhythmias by Holter monitorization in 52 cancer patients with bone metastasis before ZA and in the day of infusion. In this study, supraventricular (SVT) and ventricular tachycardia (VT) has been detected in 46% of the patients before ZA. During ZA infusion, SVT and VT have been detected in the ratio of 28.8 and 26.9%, respectively. By the 19th hour of ZA infusion, these ratios have risen to 92.3 and 78.8%, respectively. Mobitz type 2 block has been monitored in two patients as well (25). This study was analogous to ours because it was performed in cancer patients with bone metastasis. However, the fact that there were SVT and VT episodes in holter records in aproximately 50% of the patients before the drug infusion, gives rise to thought that ZA infusion may prominently trigger arrhythmia in those with the risk of arrhythmia. Again in the study of Yazici et al., most of the patients have been treated with agents which may cause cardiac damage such as anthracycline in the period before bone metastasis. In our study, patients did not have a history of chemotherapy beforehand, and there were no arrhythmias detected in their basal ECG. Also in this study, arrhythmia predictor parameters of ECG such as P disp, P min, P max, QT disp were not monitored.

In a study of 124 cancer patients with bone metastasis, Arslan et al. investigated the frequency of arrhythmias due to the use of ZA over one year. In this study, AF was not detected in any patients. Only SVT in 15% and ventricular extrasystole in 5.7% was observed. In this study giving results analogous to ours but parameters such as P disp and QT disp were not monitored (26).

Cardiac arrhythmias are often caused by one of these following three mechanism; abnormal automaticity, triggered activity, and reentry (27). Reentry mechanism is the most common responsible mechanism for arrhythmias such as SVT and VT. Anatomical and electrical pathology is required to form a reentrant tachycardia. These can occur due to fibrosis, drugs or hormonal effects (27, 28). Chronic ZA using may provoke intracellular myocardial electrical imbalance or increase the reentry mechanism, and in this way arrhythmia mechanism of ZA could be explained, but in the acute period, these mechanisms may probably trigger arrhythmias in the presence of an underlying cardiac damage.

In conclusion, the point of view that bisphosphonates trigger cardiac arrhythmia is still a controversial issue. Contradictory results are due to the fact that the patient groups are heterogeneous, that is chemotherapies received beforehand, underlying cardiac diseases etc. In our study, underlying cardiac abnormalities were excluded by echocardiography and there was no history of chemotherapy. Our study shows that there were no significant alterations in ECG in the acute period, indicated that ZA had no arrhythmia potential in the early period in patients with no underlying cardiac disease. However, patients receiving ZA should be monitored more closely because of the risk of arrhythmia which may ensue due to hypocalcemia, hypomagnesemia, or other chemotherapeutics.

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