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# A Single-Center Prospective Study of 116 Women with Osteoporosis Treated with Zoledronic Acid Monitored by Electrocardiography for the Development of Cardiac Arrhythmia During the Acute Phase in China

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**Background:** Concerns have been raised among clinicians and patients about the cardiovascular risks of bisphosphonates used in the treatment of osteoporosis. The goal of this study was to investigate the acute effect of zoledronic acid (ZA) infusion on arrhythmia development using an electrocardiograph (ECG).

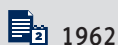
**Material/Methods:** This prospective study was a self-controlled case series study that recruited 116 female patients with osteoporosis. The patients underwent standard 12-lead electrocardiography before and 1 day after zoledronic acid intravenous infusion to evaluate cardiac adverse effects and the change in ECG parameters after the infusion. Heart rhythm, atrial and ventricular premature contractions, atrial fibrillation, P wave, and QTc parameters were measured using an ECG. A blood biochemical examination was performed for all patients before the ZA infusion. Body temperature was measured twice per day.

**Results:** Before ZA administration, ECG findings were normal in 47 patients and abnormal in 69 patients. After ZA administration, ECG findings were normal in 35 patients and abnormal in 81 patients. New onsets of premature atrial contractions and atrial fibrillation were observed in 1 patient each, and new onsets of premature ventricular contractions were observed in 2 patients. The heart rate was obviously higher, and the QT interval was obviously shorter after ZA administration, compared with before administration. No significant differences in P wave and QTc parameters were found between the 2 ECG measurements.

**Conclusions:** During the acute phase, 116 women with osteoporosis who were treated with zoledronic acid infusion did not develop significantly abnormal ECG changes.

**Keywords:** **Atrial Fibrillation • Electrocardiography • Osteoporosis**

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## Background

Osteoporosis is common among the elderly population and often leads to fragility fractures, including vertebral fracture, distal radius fracture, proximal humerus fracture, and hip fracture. The main goal of osteoporosis treatment is the prevention of fractures. According to the Clinical Guidelines Committee of the American College of Physicians, bisphosphonates are the most commonly used drugs for the treatment of osteoporosis and significantly reduce the risk of fracture [1,2]. Zoledronic acid (ZA) is a bisphosphonate widely prescribed for patients with osteoporosis, which significantly increases bone mineral density and reduces fracture risk in patients with osteoporosis. However, the incidence of arrhythmia and serious atrial fibrillation (AF) was high in patients who received an intravenous infusion of ZA in the HORIZON Pivotal Fracture Trial [3]. The findings are similar with other bisphosphonates. AF occurred in 1.5% of women treated with alendronate and in 1.0% of women taking the placebo in the Fracture Intervention Trial [4]. Another study found that extending the use of ZA to 9 years still slightly increases the arrhythmia of patients (combined severe and non-serious cases) [5,6]. Concerns have been raised among clinicians and patients about the cardiovascular risks of bisphosphonates. Therefore, this prospective study was conducted during the acute phase at the Second Affiliated Hospital of Fujian Medical University in China and included 116 women with osteoporosis who were treated with ZA infusion and monitored with an electrocardiograph (ECG) for the development of acute cardiac arrhythmia. This study aimed to evaluate the relationship between the early effects of ZA intravenous infusion and AF in patients with osteoporosis by using ECG parameters.

## Material and Methods

In this study, 116 female patients with osteoporosis were evaluated prospectively for AF and changes in ECG parameters after the intravenous infusion of ZA. The study was carried out in the Second Affiliated Hospital of Fujian Medical University between March 2018 and March 2019. Our inclusion criteria for the study were primary osteoporosis, age  $\geq 50$  years, and intravenous infusion of 5 mg of ZA. Exclusion criteria were secondary osteoporosis, bone metastases, severe arrhythmias, use of an antiarrhythmic drug, and severe ischemic heart disease. The age of the patients ranged from 52 to 92 years, with an average age of  $69.6 \pm 9.5$  years. The body mass index (BMI) of the patients was 16.0 to 27.8 kg/m<sup>2</sup>, with an average BMI of  $23.1 \pm 3.5$  kg/m<sup>2</sup>. A fasting blood sample (3 mL) was taken for blood biochemical laboratory testing. Body temperature was measured 2 times per day. All patients had a daily dose of 800 IU vitamin D and 600 mg calcium for 2 weeks before ZA administration. Saline (500 mL) was administered first, followed

by an intravenous infusion of 5 mg of ZA for 30 min. No patients had previously received anti-osteoporosis treatment. Some patients who had hypertension or diabetes continued to take medication throughout the ZA treatment.

## Bone Mineral Density Measurement

Bone mineral density was measured by a Hologic Discovery A DXA bone mineral densitometer in the standard position with machine accuracy  $<1\%$  and a 0.25% coefficient of variation. In accordance with the World Health Organization diagnostic criteria, bone mineral density of the femoral neck  $T \leq -2.5$  was defined as osteoporosis.

## ECG Measurement

Standard 12-lead ECG recordings were used as measurements. ECG recordings were performed a day before the intravenous infusion of 5 mg of ZA and repeated the day after ZA administration. ECG recordings were taken at the rate of 25 mm/s with a standard voltage of 0.1 mv/mm. The obtained ECG recordings were transferred to a computer as image files through the scanner. Heart rhythm, premature atrial and ventricular contractions, AF, P wave, and QTc parameters were measured on ECG.

## Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (SPSS, Inc, Chicago, IL, USA). Measurement data were expressed as mean  $\pm$  standard deviation. Quantitative data of the same patients before and after ZA administration were analyzed by the paired-sample *t* test.  $P < 0.05$  was considered statistically significant. The statistics of count data were evaluated by the chi-square test of row multiplication.

## Results

All patients had a body temperature below 37°C (range, 36.1°C to 36.9°C, with an average of  $36.4 \pm 0.3$ °C) before ZA administration. Because of acute phase symptoms, patient temperature after ZA administration was 36.1°C to 40.0°C, with an average of  $36.8 \pm 0.6$ °C, and 21 patients had a temperature higher than 37°C the day after ZA administration. All patients had a normal range of electrolytes, creatinine, and urea nitrogen before ZA infusion (Table 1).

## ECG Evaluation

Before ZA administration, the ECG parameters were normal in 47 patients and abnormal in 69 patients. After ZA administration, the ECG parameters were normal in 35 patients and

**Table 1.** Clinical and biochemical data of the study population.

Female patients	116
Age (years)	69.6±9.5
BMI (Kg/m <sup>2</sup> )	23.1±3.5
Serum calcium level (mmol/L)	2.27±0.12
Serum potassium level (mmol/L)	4.08±0.46
Serum sodium level (mmol/L)	140.5±2.7
Serum phosphorus level (mmol/L)	1.21±0.21
Serum magnesium level (mmol/L)	0.89±0.09
Serum creatinine level (umol/L)	61.9±14.39
Blood urea nitrogen level (mmol/L)	5.18±1.49
Bone mineral density at lumbar spine (g/cm <sup>2</sup> )	0.667±0.123
T-score at lumbar spine	-3.3±1.09
Bone mineral density at femoral neck (g/cm <sup>2</sup> )	0.549±0.106
T-score at femoral neck	-2.7±0.96

BMI – body mass index.

abnormal in 81 patients (Table 2). Of the 116 patients (13.8%), 16 showed significant changes on ECG evaluation. Frequent premature atrial contractions disappeared in 2 patients after ZA administration. New onsets of premature atrial contractions, AF, and atrioventricular block were observed in 1 patient each;

premature ventricular contractions and left anterior branch blocks in 2 patients each; and ST- or T-wave changes in 7 patients after ZA administration (Table 2).

### ECG Measurement

Heart rate was significantly higher, and QT interval was significantly shorter after ZA administration, compared with before administration ( $P<0.05$ ) (Table 3). These phenomena can be attributed to the increase in body temperature after ZA administration. No significant differences in P wave and QTc parameters were observed between the 2 ECG measurements ( $P>0.05$ ) (Table 3). P wave dispersion (PWD) might have been associated with premature atrial contractions because the PWD became shorter in the 2 patients whose premature atrial contractions disappeared, and it became longer in the 1 patient who had a new occurrence of premature atrial contractions after ZA administration. QTc dispersion was possibly associated with premature ventricular contractions because QTc dispersion became longer in the 2 patients with new occurrence of premature ventricular contractions after ZA administration.

### Discussion

Our study results showed no obvious increase in abnormal ECG findings after ZA infusion. The ECG measurement results showed that heart rate was higher and QT interval was significantly shorter after ZA administration compared with before administration; however, these changes were associated

**Table 2.** Electrocardiogram findings of patients before and after zoledronate administration.

	Before zoledronate administration	After zoledronate administration	p
Normal ECG	47	35	0.099
Abnormal ECG	69	81	
Sinus arrhythmia	13	13	
Sinusal tachycardia	2	9	
Sinusal bradycardia	9	2	
Atrial premature	6	5	
Ventricular premature	1	3	
Atrial fibrillation/flutter	0	1	
branch block	2	4	
Atrioventricular block	0	1	
Left ventricular hypertrophy	6	6	
ST or T Wave change	30	37	

ECG – electrocardiograph;  $P<0.05$ .

**Table 3.** Comparison of ECG parameters before and after zoledronate administration.

	Before administration	After administration	t value	P value
Heart rate	75.2±12.2	79.7±13.7	3.232	0.002
P wave max (ms)	105.5±10.5	103.9±10.7	1.624	0.107
P wave min (ms)	78.7±11.7	76.8±12.2	1.761	0.081
P wave dispersion (ms)	26.7±9.2	27.1±8.7	0.385	0.701
PR intervals, (ms)	153.3±17.9	155.2±18.4	1.122	0.264
QRS durations (ms)	88.0±7.2	86.9±7.3	1.787	0.077
QT (ms)	382.6±29.4	373.4±33.3	2.823	0.006
QTc max (ms)	429.3±22.3	429.8±22.8	0.269	0.789
QTc min (ms)	397.3±22.6	399.2±21.1	0.972	0.333
QTc dispersion (ms)	32.0±11.5	30.7±10.2	1.073	0.286

ECG – electrocardiograph.

with the increase in body temperature. No significant differences in P wave and QTc parameters were found between the repeated ECG measurements. One patient had AF after ZA administration.

AF is a common and serious arrhythmia among older adults and is associated with increased risks of cardiovascular and cerebrovascular complications [7]. In the European Union in 2010, the number of adults aged 55 and over with AF comprised 1.8% of the total population, and this number could increase to 3.5% by 2060 [8]. The increased risk of AF has been noted with the use of bisphosphonates, especially with ZA [3,4]. However, some research results contradicted this finding. Rhee et al [9] reported that bisphosphonates exert a protective effect against AF in older Korean women with osteoporosis. Some meta-analyses suggested that while some data link bisphosphonates to serious AF, the heterogeneity of the existing evidence and paucity of information on some of the agents preclude any definitive conclusions on the exact nature of the risk [10,11]. Plausible evidence to explain the relationship between bisphosphonate use and the development of AF is lacking. The potential mechanisms of AF associated with bisphosphonate use include the arrhythmogenic effect by reducing serum levels of calcium and phosphate, release of proinflammatory cytokines, and influence on atrial remodeling by inducing zinc-dependent matrix metalloproteinases [12,13]. To study the direct cause-effect relationship between ZA usage and AF, İlgezdi et al [14] used 24-h Holter monitoring systems to evaluate the acute effects of ZA infusion on the risk of cardiac arrhythmia and observed no episodes of AF in any patient on the day of ZA infusion. However, atrial ectopy increased in 5 patients, which might be related to alterations in cardiac autonomic activity.

PWD is an important parameter that indicates a greater tendency of the appearance of supraventricular arrhythmias, particularly paroxysmal AF. Electrocardiographic PWD reflects inhomogeneous atrial conduction and is an independent risk factor and predictor of AF [15]. The normal value of PWD is 29±9 ms, and a PWD value close to 40 ms is considered increased. Increased PWD, a marker of AF risk, could be present in cardiovascular disorders such as hypertension, cardiac heart failure, mitral stenosis, cardiac surgery, and hypertrophic cardiomyopathy [16]. ZA shortened the left atrial action potential duration and effective refractory period and increased PWD in an ex vivo perfusion study on guinea pig hearts [17]. Aktas et al [18] reported that ZA infusion does not affect PWD in patients with osteoporosis at the immediate post-infusion period and 1 month after infusion. All patients in the present study had normal PWD values before and after ZA infusion. However, PWD became shorter in the patients with the disappearance of premature atrial contractions and longer in the patients with new occurrences of premature atrial contractions after ZA administration. The association of QT values and arrhythmia susceptibility has been studied. The risk of malignant arrhythmias and sudden death are associated with an aberrant QT interval. The QT interval reflects the electrical depolarization and repolarization of both ventricles. QT dispersion values have been assumed to be a dispersion index of ventricular recovery times [19]. QTc is a marker of ventricular repolarization. Available population studies suggest that the normal QTc value for men is between 350 and 450 ms, and the normal value for women is between 360 and 460 ms [20]. Priori et al suggested a QTc cutoff value of 500 ms in patients with congenital long QT syndrome [21]. This threshold is reasonable for patients with acquired long QT syndrome [22].

The prolonged QTc interval is related to non-sustained polymorphic ventricular tachycardia and an increased risk of AF [23,24].

Magnano et al [25] confirmed that QT interval variations precede the onset of AF and that QTc, QT, and QTc variability show significant changes (greater or less than 10%) in the 30 s before the onset of AF. Drug-induced long QT syndrome is common, with more than 150 drugs already identified as causing it. The risk of developing arrhythmias is higher with the concomitant use of multiple QT-prolonging drugs [26]. Aktas et al [16] reported that QT values increase early after ZA infusion, but parameters reflecting disparity of ventricular recovery times and transmural dispersion of ventricular repolarization showed no significant differences. Our results conflicted with those of Aktas. In the present study, the QT interval was significantly shorter, and other QTc values were not significantly changed after ZA administration. However, 2 patients with new occurrences of ventricular premature contractions had greater QTc dispersion values after ZA administration compared with before administration, although the QTc dispersion values were within a normal range. One patient had AF after ZA administration in our series. The patient had normal PWD, QT interval, and QTc values, and the changes in QTc, QT, and QTc variability in the 30 s before the AF onsets were less than 10% compared with the ECG findings before ZA administration. Our

results showed no significant alterations in ECG findings and indicated that ZA had no arrhythmia potential in the early period after ZA infusion. However, some patients receiving ZA had arrhythmia, which may have been due to hypocalcemia, hypomagnesemia, or underlying heart diseases.

The small sample size is the main limitation of this study. The use of standard 12-lead ECG recordings to evaluate the acute effects of ZA infusion on the risk of cardiac arrhythmia was convenient but possibly reduced the accuracy of ECG monitoring. Increasing the number of ECG measurements in different periods after ZA infusion could result in more discoveries.

## Conclusions

This prospective study was conducted at a single center in China. During the acute phase, 116 women with osteoporosis were treated with ZA infusion. One patient had AF after ZA administration. However, no patients developed significantly abnormal ECG changes.

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