Acute effect of zoledronic acid infusion on atrial fibrillation development in patients with osteoporosis

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Abstract

Objective: There is ongoing controversy related to the relationship between bisphosphonates and atrial fibrillation (AF). Our aim in this study was to evaluate the potential acute effect of zoledronic acid (ZA) infusion on AF development by using 24-hour Holter recordings.

Methods: The study was designed to be a self-controlled case series study, and 33 consecutive patients with osteoporosis (29 females, age: 62.3±9.0 years) who were scheduled to receive ZA infusion constituted the study population. Patients underwent 24-hour Holter rhythm recordings at two different times; the first one was 48 hours before the planned ZA infusion, and the second one was on the morning of the infusion day. Heart rate, frequency and type of arrhythmias, as well as heart rate variability (HRV) from the two recordings were compared.

Results: There were no episodes of AF greater than 30 sec in any of the 24-hour Holter recordings obtained before and on the day of drug infusion. Holter recordings before drug infusion showed that only 1 patient had an atrial run of 3 beats long. Holter recordings obtained on the day of drug infusion revealed that 5 patients (15.2%) had atrial runs with lengths ranging between 3 and 12 beats (p=0.046). Regarding HRV variables, SDANN values were found to be significantly depressed on the day of ZA infusion (113.6±26.9 vs. 98.2±29.9, p=0.007).

Conclusion: None of the patients developed AF during or early after ZA infusion. However, there was an increase in atrial ectopy in some patients, which might be due to alterations in cardiac autonomic activity. *(Anatol J Cardiol 2015; 15: 320-4)*

Keywords: osteoporosis, zoledronic acid, atrial fibrillation, 24-hour Holter recording

Introduction

Osteoporosis is a common health problem of elderly people, with a number of important consequences, including back pain, disability, and death (1). Bisphosphonates are commonly used in the management of osteoporosis. However, frequent and complex administration of oral bisphosphonates compromises the utility of these agents (2). Zoledronic acid (ZA) is a bisphosphonate that allows annual treatment in postmenopausal patients affected by osteoporosis or at high risk of fracture. The availability of annual administration and the favorable tolerability has made ZA a comfortable and efficacious treatment option for these patients (3).

The efficacy of once-yearly, 15-minute infusion of ZA on fractures caused by osteoporosis was investigated in two large-scaled multicenter randomized trials. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly- Pivotal Fracture Trial (HORIZON-PFT) (4) and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly- Recurrent Fracture Trial (HORIZON-RFT) (5) demonstrated the efficacy of once-yearly infusion of ZA, with significantly reduced rates of vertebral and hip fractures compared to placebo.

Atrial fibrillation (AF) has been reported to be more commonly seen as a serious adverse event compared to placebo in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT). Most of the patients in the ZA group in whom AF was reported as a serious event developed AF-related symptoms more than 30 days after the infusion (4). These observations prompted researchers to investigate the possible link between bisphosphonate therapy and AF; however, subsequent studies have shown conflicting results (6).

The aim of the present clinical study was to investigate the acute effect of ZA infusion on AF occurrence by using 24-hour rhythm Holter recordings in a population of patients with osteoporosis.

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Methods

Study design and patients

The study was designed as to be a self-controlled case series study. Consecutive patients with osteoporosis who were admitted to our clinic between September 2011 and May 2012 and scheduled to receive ZA infusion constituted our study population (n: 49; 39 females, age: 65.4±8.3 years). A detailed medical history, physical examination, and serum biochemistry were obtained from all patients. Serum calcium, phosphorus, and parathyroid hormone (PTH) levels were also screened for all patients. Parathyroid hormone is a regulatory hormone of calcium homeostasis, and its level increases in the presence of hypocalcemia. Serum PTH level increases as a result of a decrease in serum calcium level in the presence of vitamin D deficiency, which is called secondary hyperparathyroidism. We evaluated all osteoporotic patients for the presence of hypocalcemia and hyperparathyroidism, because treatment with bisphosphonates is known to inhibit bone resorption and increase the tendency for hypocalcemia. All patients underwent a baseline transthoracic echocardiographic examination. Patients with chronic AF, more than mild valvular disease on echocardiography, left ventricular systolic dysfunction (ejection fraction <60%), chronic renal failure, serious electrolyte imbalance, and hyper- or hypothyroidism were excluded from the study. Other exclusion criteria were a history of intravenous bisphosphonate therapy at any time and oral bisphosphonate therapy within 3 months before enrollment into the study. Patients taking any anti-arrhythmic agent, such as a beta-blocker and calcium channel blocker, were also excluded. After exclusion, 33 remaining patients with osteoporosis (29 females, age: 62.3±9.0 years) underwent 24-hour Holter rhythm recordings at two different times: the first recording was started 48 hours before the planned day of ZA infusion and the second was started on the morning of the infusion day. At the time that the Holter ambulatory recordings were commenced, all patients were given intravenous infusion therapy. Heart rate, frequency and type of arrhythmias, as well as heart rate variability from the two recordings were compared. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

24-hour Holter recordings

Recordings were obtained using 3-channel analog recorders (VX3 Holter System) and analyzed by a blinded observer using the Biomedical Systems Century Series C1000 software (version 2.13). Paroxysmal AF was defined as paroxysms of AF lasting for at least for 30 seconds (7). The time domain analysis of heart rate variability (HRV) was performed according to the recommendations of the European Society of Cardiology task force (8). The mean heart rate, standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN), root mean square of successive differences (RMSSD), and HRV triangular index (TRIA) were measured in the time domain analysis of HRV. SDNN and HRV triangular index have been assumed to reflect overall HRV, SDANN has been assumed to reflect the long-term components of HRV, and RMSSD has been assumed to reflect its short-term components. A reduced SDNN has been considered to reflect diminished autonomic modulation of the sinus node.

Statistical analysis

Statistical analysis was performed using SPSS for WINDOWS (version 15.0; SPSS Inc., Chicago, Illinois, USA). The distribution of data was assessed using one-sample Kolmogorov-Smirnov test. Ordinal variables displaying normal distribution were expressed as mean±SD, and ordinal variables not displaying normal distribution were expressed as median (interquartile range). Differences regarding the frequency of atrial and ventricular arrhythmias observed on the Holter recordings before and on the day of ZA infusion were evaluated with Wilcoxon signed-rank test. Differences between HRV variables between two Holter recordings were evaluated with paired-samples student t-test. A p value less than 0.05 was considered significant.

Results

Data on 33 patients were used in the analysis. The clinical and biochemical data of these patients are displayed in Table 1. Fifteen patients (45.4%) had intact serum parathyroid hormone (PTH) levels above the normal range (normal range, 12-72 pg/mL), whereas only 2 patients (6%) had serum calcium levels above the normal range (normal range 9-10.5 mg/dL), and 1 patient (3%) had serum phosphate levels below the normal range (normal range: 2.4-4.1 mg/dL). All patients had serum magnesium levels within the normal range. The transthoracic echocardiographic findings of patients are presented in Table 2.

A total of 3483 premature ventricular contractions (PVCs) and 44 supraventricular premature contractions (SVPCs) were recorded in the Holter recordings obtained before ZA infusion. On the other hand, 6858 PVCs and 194 SVPCs were recorded in the Holter recordings obtained on the day of drug infusion (p=0.9 for PVCs and p=0.05 for SVPCs). There were no episodes of atrioventricular blocks or pauses in any of the Holter recordings.

There were no episodes of sustained (lasting more than 30 seconds) or nonsustained ventricular tachycardia in any of Holter recordings obtained before and on the day of drug infusion. Nine (27.2%) patients displayed PVCs on Holter recordings obtained before drug infusion, whereas 10 patients (30.3%) displayed PVCs on Holters obtained on the day of drug infusion (p=0.90). Eight patients displayed PVCs on both Holter recordings; 1 patient displayed PVCs only on the Holter obtained before infusion, and 2 patients displayed PVCs only on the Holter obtained on the day of infusion. The frequency of PVCs was less than 10% of total heart beats for each patient displaying PVCs on the Holter recordings.

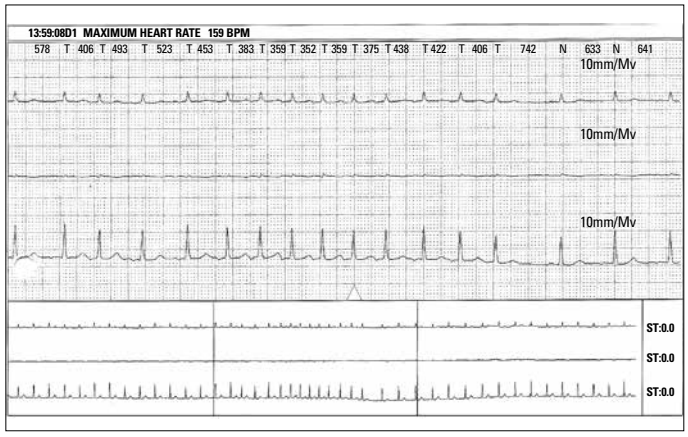

Figure 1. Representation of an atrial run of 12 beats long obtained from a Holter recording on the day of drug infusion

Table 1. Clinical and biochemical data of study population

Age, years	62.3±9.0
Sex, male/female	4 M, 29 F
Serum PTH level (mean±SD, pg/mL) (normal: 10-55 pg/mL)	75.9±42.9
Serum TSH level (mean±SD, mIU/L) (normal 0.4-4.2 mIU/L)	2.1±0.8
Serum calcium level (mean±SD, mg/dL) (normal: 8.5-10.2 mg/dL)	9.57±0.49
Serum phosphorus level (mean±SD, mg/dL) (normal 2.4-4.1 mg/dL)	3.41±0.64
Serum magnesium level (mean±SD, mg/dL) (normal: 1.7-2.2 mg/dL)	1.95±0.15
Serum creatinine level (mean±SD, mg/dL) (normal: 0.6-1.2 mg/dL)	0.68±0.13
Blood urea nitrogen level (mean±SD, mg/dL) (normal 6-20 mg/dL)	12.3±4.0
Serum sodium level (mean±SD, mEq/L) (normal 135-145 mEq/L)	139.5±1.8
Serum potassium level (mean±SD, mEq/L) (normal 3.7-5.2 mEq/L)	4.4±0.3
Hypertension, n (%)	5 (15%)
Diabetes mellitus, n (%)	6 (18.7%)
Hyperlipidemia, n (%)	5 (15%)
Smoking, n (%)	2 (6%)

PTH - parathyroid hormone; SD - standard deviation; TSH - thyroid-stimulating hormone

There were no episodes of AF episode, which was defined as more than 30 sec in duration, in any of the 24-hour Holter recordings obtained before and on the day of drug infusion. Pre-infusion Holter recordings showed that only 1 patient had an atrial run of 3 beats long, whereas Holter recordings obtained on the day of drug infusion revealed that 5 patients (15.2%) developed atrial runs between 3 and 10 beats (p=0.046). One patient had 2 atrial runs (3 and 12 beats long) (Fig. 1), and others had only one atrial run on the 24-hour Holter recording obtained on the day of drug infusion (Table 3). None of these 5 patients had hypertension, diabetes mellitus, or smoking habit. Transthoracic echocardiographic examinations of these 5 patients demon-

Table 2. Transthoracic echocardiography variables of the study population

LV end-diastolic diameter (mean±SD, mm)	37.9±3.9
LV end-systolic diameter (mean±SD, mm)	22.8±2.8
LV ejection fraction (mean±SD, %)	65.1±3.9
Aortic diameter (mean±SD, mm)	24.0±2.9
Left atrial diameter (mean±SD, mm)	32.6±2.8
Transmitral E velocity (mean±SD, cm/s)	0.68±0.15
Transmitral A velocity (mean±SD, cm/s)	0.79±0.15
Septal end-diastolic thickness (mean±SD, mm)	0.93±0.1
Posterior wall end-diastolic thickness (mean±SD, mm)	0.92±0.08
Mitral regurgitation (mild), n (%)	7 (21.2%)
Aortic regurgitation (mild), n (%)	6 (18.2%)
Tricuspid regurgitation (mild), n (%)	7 (21.2%)

LV - left ventricle; SD - standard deviation

Table 3. Number and durations of atrial runs observed on 24 hour recordings obtained before and on the day of drug infusion

Age	Before drug infusion	On the day of drug infusion
63	1 atrial run of 3 beats long	1 atrial run of 4 beats long
81	------	1 atrial run of 6 beats long
60	------	1 atrial run of 7 beats long
61	------	2 atrial runs; 3 and 12 beats long
58	------	1 atrial run of 3 beats long

Table 4. Heart rate variability variables obtained before and on the day of drug infusion

	Before drug infusion	On the day of drug infusion	Variation	*P*
Maximum heart rate (mean±SD)	123.9±16.1	124.6±11.9	-0.6±21.8	0.87
Minimum heart rate (mean±SD)	50.3±5.5	52.9±5.6	-2.6±4.7	0.004
Mean heart rate (mean±SD)	72.8±6.9	75.0±7.9	-2.2±8.8	0.16
SDNN (mean±SD)	146.8±39.1	136.9±61.4	9.9±69.9	0.42
SDNN5 (mean±SD)	78.9±45.7	81.2±64.4	-2.3±80.2	0.87
SDANN (mean±SD)	113.6±26.9	98.2±29.9	15.42±30.50	0.007
pNN50 (mean±SD)	16.5±9.6	16.9±13.3	-3.3±15.9	0.9
TRIA (mean±SD)	551.4±169.6	500.3±143.6	51.0±196.9	0.15
RMSSD (mean±SD)	82.3±55.3	79.7±63.6	2.6±85.5	0.86

SD - standard deviation; TRIA - triangular index

strated normal-sized left atria for each patient, without any valvular regurgitation or stenosis. Regarding HRV variables, only the difference between SDANN values of two Holter recordings was found to be statistically significant (Table 4).

Discussion

The principle finding of the present study is that there is no increase in the frequency of AF and ventricular arrhythmias on the day of ZA infusion. However, there was a statistically significant increase in the frequency of atrial runs only in 5 patients.

The association between bisphosphonate therapy and AF is mainly derived from serious adverse event (SAE) reports from clinical trials, observational studies, and meta-analyses (6, 9). The observation of an association between ZA therapy and increased risk of AF in HORIZON-PFT raised concerns about arrhythmogenic effects with the use of bisphosphonates, although there was no excess risk of cardiac arrhythmias in patients treated with ZA in HORIZON-RFT (4, 5). A review of the Fracture Intervention Trial (FIT), which was published as a letter to the editor after the publication of the results of HORIZON-PFT, revealed a nominally but not significantly increased risk of AF events with alendronate-treated patients compared to placebo (10). After publication of those reports, meta-analyses of clinical trials have been conducted and retrospective studies have been performed to examine the risk of AF in patients taking bisphosphonates for the treatment of osteoporosis. In most of the meta-analyses and reviews, bisphosphonate use was not associated with an increased risk of AF (6, 9, 11). However, it was difficult to reach a definitive conclusion, since there were no available data gathered from prospective studies directly evaluating effects of bisphosphonates on cardiac arrhythmias. Both osteoporosis and AF usually occur together in elderly people (12). As such, it is difficult to suggest a direct cause-effect relationship between bisphosphonate usage and AF because of the general AF risk in elderly patients. Because of confounding factors, we planned our study by comparing the Holter recordings within the same individuals before and during, as well as after, the infusion period.

Zoledronic acid is also used for the treatment of bone metastasis and multiple myeloma. Cumulative ZA dosages of cancer patients with bone metastasis are higher compared with the dosage used in osteoporosis. In a recent study, Yazıcı et al. (13) evaluated the arrhythmogenic effects of ZA infusion in cancer patients with bone metastasis by using 24-h Holter recordings obtained during the first dose ZA infusion day. They reported increased atrial and ventricular premature complexes during and after ZA infusion compared to basal recordings obtained before drug infusion. However, Arslan et al. (14) did not demonstrate an increased risk of AF in a similar study population, using standard 12-lead electrocardiography (ECG) recordings.

The mechanism of a possible association between bisphosphonates and AF is not well established. Acute changes in myocardial cellular electrolyte homeostasis, particularly involving Ca+2, Mg+2, and Cl-, might have been implicated as contributing factors for atrial ectopy (6). It has been proposed that intracellular electrolyte imbalances may lead to functional abnormalities in the cardiomyocyte and cause reentry or increased automaticity (13). This hypothesis raises the question of whether frequent monitoring and prompt correction of electrolyte abnormalities cure ZA-related AF. However, most of the AF events occurred more than 30 days after the infusion in HORIZON-PFT (4), and longer-term proinflammatory, profibrotic, and antiangiogenic effects of bisphosphonates have been accused of contributing to AF (6).

SDANN values are suggested to reflect longer-term components of HRV. SDANN values were found to be depressed on the day of infusion compared to recordings obtained before the infusion, which may imply that alterations in autonomic nervous system activity may also be operative for the increased atrial ectopy in our patients. On the other hand, the depression of SDANN found in our study on the day of drug infusion might be related to increased anxiety of intravenous cannulation and infusion.

Study limitations

The small sample size is the main limitation of this study. We used 24-hour Holter monitoring systems to evaluate the acute effects of ZA infusion on the risk of cardiac arrhythmia. As most of the AF events were reported to occur 30 days after drug infusion in previous studies, it might have been more valuable to use event recorders with longer-term recording capability.

Conclusion

There were no episodes of AF in any patient on the day of ZA infusion. However, there was an increase in atrial ectopy only in 5 patients, which might be related to alterations in cardiac autonomic activity. Results of prospective studies using systems with longer-term recording capability are required to elucidate the effects of ZA infusion on the risk of AF.

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