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Original Article / Özgün Araştırma

Should the cardiac rhythm be monitored following administration of zoledronic acid in elderly osteoporotic women?

Yaşlı osteoporotik kadınlarda zoledronik asit uygulaması sonrası kalp ritmi takip edilmeli midir?

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ABSTRACT

Objectives: This study aims to investigate the possible undesirable cardiac effects associated with zoledronic acid treatment in elderly osteoporotic women.

Patients and methods: Between October 2010 and December 2013, a total of 33 osteoporotic female patients (mean age 73.3±6.9 years; range 65 to 85 years) were included in this prospective study. Bone mineral density of the patients was measured. Biochemical and hormonal analyzes were performed. Electrocardiograms were taken. These analyses were repeated twice at one hour and 10 days after the administration of the zoledronic acid.

Results: Pre- and post-treatment electrocardiography findings within the first hour were found to be within normal limits. P-wave dispersion and RR intervals, which were found to be normal before administration of the drug, tended to significantly increase at 10 days following the administration (p=0.029 and p=0.031, respectively). Using a cut-off value of 50 msec, alterations in corrected QT dispersion were found to be statistically significant (p=0.004).

Conclusion: Based on our study findings, an increased ventricular arrhythmia risk should be also possibly considered as well as well-known atrial arrhythmic adverse effects of zoledronic acid. Therefore, we recommend a thorough examination for cardiac arrhythmia before the drug administration.

Keywords: Adverse effect; cardiac arrhythmia; osteoporosis; toxicity; zoledronic acid.

ÖZ

Amaç: Bu çalışmada osteoporotik yaşlı kadın hastalarda zoledronik asit tedavisi ile ilişkili olası istenmeyen kardiyak etkiler araştırıldı.

Hastalar ve yöntemler: Ekim 2010 - Aralık 2013 tarihleri arasında, toplam 33 osteoporotik kadın hasta (ort. yaş 73.3±6.9 yıl; dağılım, 65-85 yıl) bu prospektif çalışmaya alındı. Hastaların kemik mineral yoğunluğu ölçüldü. Biyokimya ve hormon analizleri yapıldı. Elektrokardiyografileri çekildi. Bu analizler, zoledronik asit uygulandıktan bir saat ve 10 gün sonra olmak üzere, iki kez tekrarlandı.

Bulgular: Tedavi öncesinde ve tedavi sonrası birinci saatte elektrokardiyografi bulguları normal sınırlar içinde bulundu. İlaç uygulaması öncesinde normal bulunan P dalga dispersiyonu ve RR aralığında, uygulamadan 10 gün sonra anlamlı bir artış eğilimi izlendi (sırasıyla p=0.029 ve p=0.031). 50 msn.'lik eşik değeri kullanıldığında, düzeltilmiş QT dispersiyonundaki değişiklikler istatistiksel olarak anlamlı bulundu (p=0.004).

Sonuç: Çalışma bulgularımıza göre, zoledronik asidin iyi bilinen atriyal aritmik advers etkilerinin yanı sıra, ventriküler aritmi riskinde artış olasılığı da göz önünde bulundurulmalıdır. Bu nedenle, ilaç uygulanmadan önce kardiyak aritmiye yönelik kapsamlı bir inceleme önerilmektedir.

Anahtar sözcükler: Advers etki; kardiyak aritmi; osteoporoz; toksisite; zoledronik asit.

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Osteoporosis (OP) is a major public health problem that significantly affects mortality, morbidity and healthcare resources.[1] In metastatic bone cancers and osteoporotic patients' treatments, bisphosphonate agents (BPs) act on preserving bone density, preventing bone fragility, and reducing the associated mortality rate.[2-4] Medications with antiresorptive characteristics have been used to resolve this problem, which affects millions of people and can result in morbidity.[2-4]

The unexpected cardiac arrhythmias of BPs have been rarely reported as an adverse effect.[5-10] In OP patients treated with BPs, atrial fibrillation (AF) is the most common cardiac arrhythmias as an adverse effect of the drug.[11,12] The possibility of other arrhythmias, such as ventricular arrhythmia (VA), should not be ignored. This has led to the necessity of carefulness while applying BPs in OP treatment.[11,12] In this study, we aim to investigate the affect of zoledronic acid (ZA) on cardiac arrhythmia in OP.

PATIENTS AND METHODS

This prospective study was performed between 1 October 2010 and 12 December 2013. This study is in compliance with Namık Kemal University Faculty of Medicine, the Ethics Committee rules, and The World Medical Association Declaration of Helsinki, by receiving the informed consent from all patients that took part in the study. This study took place in the Central Directorate of Research and Practice, Department of Physical Medicine and Rehabilitation, Osteoporosis Follow-up Clinic.

Male and female patients were separated and female patients over 65 years of age were evaluated following an OP diagnosis according to the T-score value determined by The World Health Organization (WHO) and the International Osteoporosis Foundation (IOF) guidelines.[13-15] To determine the subjects, men were excluded (n=24), and data was used from the OP-diagnosed women who were over 65 years of age (n=309).[13-15] Blood and urine samples were taken from these patients before the ZA administration.

This was done to determine whether an adverse effect seen in patients after the ZA administration was caused by ZA or other factors. An electrocardiogram (ECG) of the patients was then taken before the ZA administration. Following the ECG, average P, QT, and RR interval durations were calculated and corrected average QT values were calculated using various formulas. The bone mineral density (BMD), ECG, and hormonal and biochemical parameters of patients who had not received any osteoporotic treatment in the last two years were evaluated. Biochemical and hormonal tests were done in the morning after eight hours of fasting during the same time intervals. These analyses were carried out before the drug administration.

The ECGs were repeated one hour after the drug administration, and 11 days after drug administration. The biochemical and hormonal test were repeated 11 days after drug administration. Patients were advised to drink at least 2,500 mL of water per day for three days before the OP treatment began. Patients were also given calcium (Ca^{2+}) and vitamin D preparations before the treatment began. These supplement preparations were given to prevent the patient from developing hypocalcaemia.[16] To exclude patients experiencing cardiac arrhythmia and to evaluate the risks of drug-associated atrial and/or ventricular arrhythmia risks, ECG tests were done. In order to, investigate how the cardiac muscle and neuronal transmission systems work, ECG data of cardiac electrical activity was recorded using a Schiller-U2 ECG electrocardiograph. Patients were evaluated twice in the supine position, at a speed of 25 mm/sec with a gauge pressure equal to 1 mV and with 12 derivations. The durations and long-term results of the ECG data were calculated by researchers using a single-blind method. To avert mistakes that may have occurred from individual differences during the physical examination, the same researcher performed the drug administration, instrumental analysis, and all other analyses. In cases where there were disputes between the authors, the data was re-evaluated and discussed until a consensus was reached.

To determine the T-scores specific to female patients, a LUNAR dual energy X-ray absorptiometry (DXA) was used to measure BMD in gr/cm^2 of sectional bone. During the measurements, patients' BMD values were calculated using a formula that compared their value to the BMD value of a young adult.[13-15] T-scores of the lumbar spine 1-4 (L1-4) and total femur (TF) were recorded.

Electrocardiogram tests were repeated before ZA administration, one hour after ZA administration, and 11 days following drug administration (Figure 1). The P, QT, and RR intervals of the patients were calculated according to the standard measurements by measuring at least three cycles and taking their average. During these calculations, in all derivations, P-wave duration was measured with its starting point taken as the intersection of the isoelectric line and the starting point of the P wave. The end point was taken as the

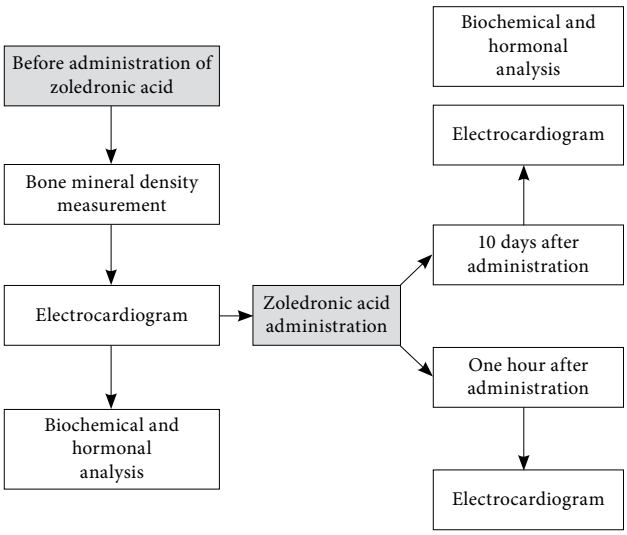

Figure 1. Study design.

intersection of the isoelectric line and the ending point of the P wave. The QT interval was measured starting from the beginning of the QRS complex to the end of the T wave. When the termination of the T wave was not clear, the site where the descending arm of the T wave intersected with the isoelectric line was considered the ending point of the T wave. To calculate the P and QT dispersion values, the maximum and minimum values of each interval in 12 derivations were recorded. In assessing the propagation of sinus impulses, where inhomogeneous conduction of the atrial myocardium, represented by P wave differences, P wave dispersion (Pd), which is a discontinuous conduction type, was calculated using the formula shown below and measured in milliseconds (ms) ($Pd= P_{max}-P_{min}$). The longest and the shortest P waves were expressed as Pmax and Pmin, respectively.[13-15]

QT dispersion (QTd) is an indicator of the increase in repolarization differences in ventricular muscle and was calculated using the formula ($QTd=QT_{max}-QT_{min}$).

QT_{max}, represents the longest QT interval and QT_{min} is the shortest QT interval.[15,17-21] However, because a predisposition to ventricular arrhythmia cannot be accurately determined with only the QTd calculation, QT intervals were verified as corrected QT (QTc) intervals using the following formula, in addition to the QTd results.[20-22] (QTc=(QT)/(RR interval)x2)

Consequently, it can be interpreted whether the QT interval was found in the expected value range or if it was abnormally prolonged, while taking into consideration the heart rate.

The QTc values under 420 ms in patients who did not receive any pharmaceutical treatment were certainly considered normal, values between 420-440 ms were considered borderline, and QTc values over 440 ms were considered high. However, studies showing that 12% of patients with hereditary long QT syndrome had QTc values between 420-440 ms should be taken into consideration.[23,24] In normal, healthy people, QTd values range between 40-50 ms and 50 ms is considered the upper limit of the normal range.[25]

We found no differences between the before ZA administration group and the after one hour ZA administration group in terms of ECG parameters ($p>0.05$). Thus, we compared ECG parameters between the before ZA administration group and the 11 days after ZA administration group.

A standard demographic table was developed and was comprised of sex, age, height, weight, BMD, alcohol and tobacco consumption, concomitant diseases, and medication(s) used. BMD T-scores for L1-4 and FT were also added to this standard form. The hormonal and biochemical parameters that were analyzed included: hemoglobin (Hb), creatinine (SCr), protein, albumin, sodium (Na^+), potassium (K^+), chlorine (Cl^-), alanine aminotransferase (ALT), calcium (Ca^{2+}), phosphorus (P^{3-}), alkaline phosphatase (ALP), parathormone (PTH), vitamin B12 and vitamin D. Analyses were also done on the erythrocyte sedimentation rates (ESR) and serum reactive protein (CRP) levels.

Additionally, biochemical tests were done, and included 24-hour urine creatinine clearance (CrCl), and elements, such as Ca^{2+} and P^{3-}. Test results were recorded to determine the following exclusion criteria; serum Hb levels under 8 g/dL, vitamin B12 levels under 200 pg/mL, 24-hour urine creatinine clearance under 50 mL/min, serum phosphorus levels over 5.5 mg/dL, PTH over 300 pg/mL and creatinine levels over 1.3 mg/dL. Other exclusion criteria included patients with anemia (n=16), renal disease (n=9), and hepatobiliary disease (n=1). Also, after the ECG analysis, cardiac and rhythm abnormalities (n=16) were excluded from the study.

After ZA administration, to ensure that possible side effects caused by ZA administration would not be confused with the side effects of routine medications, patients who were on more than one medication were excluded from the study. Some of these medications included: quinidine, amiodarone, sotalol, ketoconazole, itraconazole, miconazole, erythromycin, clarithromycin, and terfenadine, which are known to affect the QT interval or the

sympathetic nervous system (n=234).[26] With that objective in mind, OP patients who were on amino or non-amino BP treatments with effective potencies and pharmaceutical mechanisms different from ZA for the past two years were also excluded from the study.

Ultimately, a total of 300 patients, 24 because they were male and 276 due to the reasons given above, were excluded from the study. The remaining 33 female patients' parameters, before ZA administration, were recorded as part of the control group. These patients (n=33) were referred to the Outpatient Clinic (Figure 2).

A solution consisting of 5 mg of ZA (anhydrous; equivalent to 5.330 mg ZA monohydrate), mannitol, sodium citrate, and water was injected over a 30-minute period by intravenous (IV) infusion while checking the heart rate and arterial blood pressure.

Statistical analysis

The PASW Statistics version 18.0 software (SPSS Inc., Chicago, IL, USA) was used for data entry and statistical analysis. Descriptive statistics were calculated (mean, standard deviation, median, and range) after performing data control. The Shapiro-Wilk test was used to check whether the data fits a normal distribution. In cases where data was normally distributed, a t-test was used for dependent groups for comparative analysis. McNemar's test was performed to compare two dependent categorical variables. All statistical hypothesis test have been conducted at a 0.05 significance level.

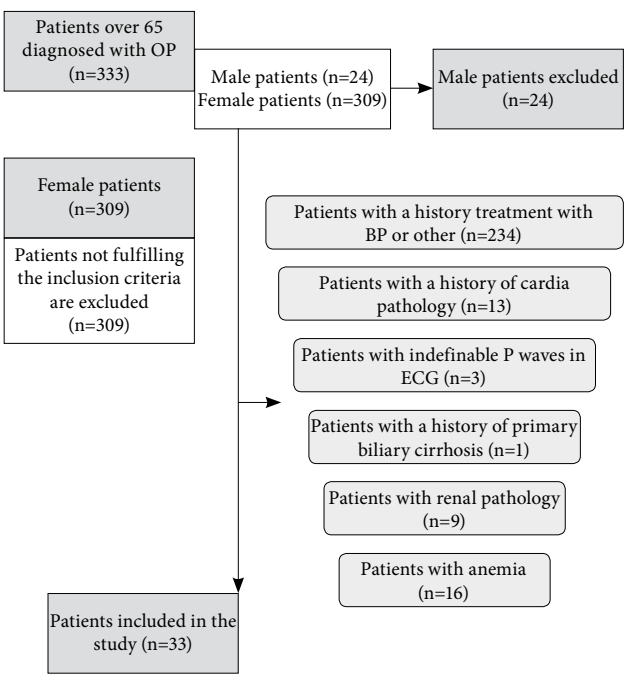

Figure 2. Inclusion and the exclusion criteria of the study.

RESULTS

The means of patients' heights, weights and body mass indexes (BMI) were recorded as 159.4±6.1 cm, 69.8±9.7 kg, and 24.6±4.6 kg/m^2, respectively (Table 1).

Serum levels of Na^+, K^+, Cl^-, Ca^{2+}, creatinine, ALP, ESR, and CRP, as well as 24-hour urine CrCl, Ca^{2+}, and P3- levels of patients before the treatment were within normal limits (Table 1).

Patients with a history of gastrointestinal complaints (n=1), compression fracture (n=4), pemphigus (n=1), rheumatoid arthritis (n=1), hypothyroidism (n=1) and cerebrovascular accident (n=1) during the pre-treatment duration were recorded. When the pre-treatment patient data and 11th day data were compared, it was determined that mean P^{3-} and PTH values were significantly different and the decrease in mean Hb values were not statistically significant (Table 2).

After ZA administration, no significant difference was observed in mean Hb values compared to the pre-treatment group; also, severe anemic cases were not detected. However, in six cases (18.2%), Hb levels were lower than 11.5 g/dL after ZA administration.

The adverse effects that patients experienced after ZA administration were recorded as flu-like symptoms (n=3), gastrointestinal complaints (n=1), and diffuse joint pain on the sixth day (n=1), and a right bundle branch block (n=1). The only adverse effect that resolved on its own at the end of the first day was the right bundle branch block. There was also one

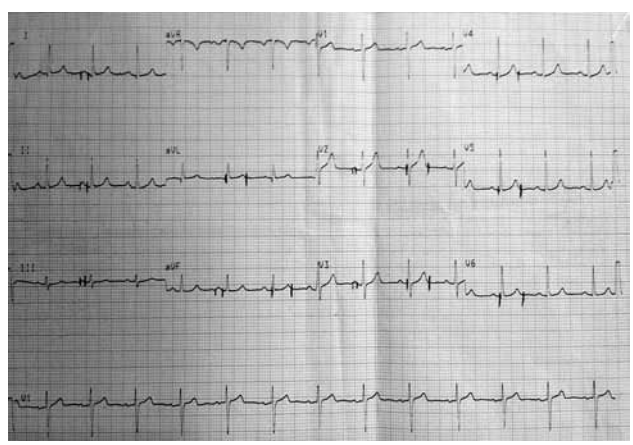

Figure 3. QT dispersion prolongation; changes in electrocardiogram data of a 69-year-old female patient.

Table 1. Demographic data and biochemical parameters of the patients

Characteristics (n=33)	Mean±SD	Median	95% CI	
			Lower	Upper
Demographic data				
Age (years)	73.3±6.9	74.0	70.89	75.77
Menopause duration (years)	25.2±8.9	26.0	22.04	28.38
Bone mineral density				
Lumbar spine 1-4	-2.0±1.3	-2.3	-2.43	-1.53
Femur neck t scores	-2.2±0.8	-2.3	-2.44	-1.87
Femoral total t scores	-2.1±0.9	-2.1	-2.43	-1.81
In 24 hour urine sample				
Ca^{2+} (mg/day)	66.1±96.3	24.0	31.95	100.25
P^{3-} (g/day)	12.4±19.8	0.60	5.37	19.43
CrCl (mL/minute)	77.3±23.5	74.9	68.95	85.59
In serum				
Vitamin D (ng/mL)	26.7±19.8	24.0	19.66	33.74
C-reactive protein (mg/L)	5.5±5.9	4.1	3.44	7.59
Erythrocyte sedimentation rate (mm/hour)	28.9±18.2	27.0	22.45	35.36
Ca^{2+} (mg/dL)	9.6±0.5	9.5	9.39	9.73

SD: Standard deviation; CI: Confidence interval.

patient who had bypass surgery following an inferior myocardial infarction with unknown etiology (n=1).

Both before, and one hour after the ZA administration, ECG data were evaluated and the findings were within the normal limits. There were no differences between the before and the one hour after ZA administration groups in terms of Pd, RR intervals, QTd and QTc. The Pd and RR intervals were longer in the 11 days after ZA administration group than the before ZA administration group (p=0.029 and p=0.031, respectively). However there were no differences between the 11 days after ZA administration group and the before ZA administration group in terms of QTd and QTc values (p=0.062 and p=0.154, respectively) (Table 3).

The cut-off value for QTc dispersion (QTcd) was determined to be 50 ms and any value higher than this point was considered abnormal. Based on these evaluations, on the 11th day following ZA administration, QTcd values that would be considered abnormal were observed and they were found to be statistically significant (p=0.004) (Table 4).

DISCUSSION

Many studies have examined the efficacy and safety of ZA administration in OP treatment.[5,10,27-29] Zoledronic acid can cause adverse dermatological reactions, hepatotoxicity, hallucinations, and gastrointestinal side effects (nausea and vomiting: 5.8% and 2.6%, respectively). It also has a wide range of adverse side effects such as local infection symptoms including osteomyelitis, osteonecrosis of the jaw and atypical femur fractures.[5,10,29] Studies performed in recent years have reported that IV administration of ZA can cause flu-like symptoms in 9% of patients.[29] Even though they were rarely observed, blood (severe anemia in 5.2% of the patients with a Hb <8.0 g/dL) and lymph system diseases, and respiratory complaints would can observed due to ZA administration. Cardiac arrhythmias are observed in ZA applied patients up to 14.1%.[30] Atrial fibrillation is the most common arrhythmia in these patients and a group of these arrhythmias would be life threatening.[30]

Electrocardiogram results are the first indication of whether or not a patient has a cardiac pathology.

Table 2. The changes of the biochemical parameters after zoledronic acid administration

Parameters	Before ZA administration			11th day after ZA administration			
	Mean±SD	Median	Min.-Max.	Mean±SD	Median	Min.-Max.	*p*
Phosphorus (mg/dL)	3.5±0.5			3.3±0.3			0.04*
Alkaline phosphatase (IU/L)	22.5±3.9			22.9±4.0			0.50*
Parathormone (pg/mL)		48.2	16-115		70	18.9-123	<0.001**
Hemoglobin (g/dL)	12.9±1.3			12.7±1.1			0.06*

ZA: Zoledronic acid; SD: Standard deviation; Min.: Minimum; Max.: Maximum; * T-test for Paired samples; ** Wilcoxon signed rank test.

Table 3. Comparison of changes in electrocardiographic parameters before zoledronic acid administration and 11 days after zoledronic acid administration

Parameters (milliseconds)	Before ZA administration	After ZA administration	
	Mean±SD	Mean±SD	*p**
Phosphorus dispersion	34.8±10.9	39.1±14.2	0.029
QT dispersion	29.7±7.3	33.9±12.7	0.062
RR interval	780.0±69.3	807.0±83.0	0.031
Corrected QT	44.6±2.5	47.6±11.7	0.154

ZA: Zoledronic acid; SD: Standard deviation; * T-test for Paired samples.

Clinicians can diagnose a patient with cardiac arrhythmia by evaluating the P, QT, QTc, Pd, QTd, and QTcd parameters found in the patient's ECG data.[31-33] Therefore, by performing an ECG test before and after ZA administration, these parameters were evaluated.

We believe the current study can contribute to the literature with its simultaneous investigation of cardiac conduction from both the AF and VA aspects in the same patient population administered ZA. No similar study has been found in the literature prior to this one.

Besides ZA-associated side effects, one cardiac arrhythmia, AF, was observed. Some sources have reported BPs associated with AF.[34] While the cause of AF after ZA administration is not clear, pro-inflammatory, pro-fibrotic, and anti angiogenic effects and intracellular electrolyte imbalance are among the suggested mechanisms.[34] In similar studies, hypocalcemia, hypomagnesemia, hypokalemia, hypophosphatemia, and increased blood creatinine and urea levels were frequently observed, whereas, in very rare cases, hyperkalemic hypernatremia has also been mentioned.[29] Also, because hypocalcaemia is a cause of QTc prolongation, and hypercalcemia is among the reasons that shorter QTc, patients with electrolyte imbalances, cardiac arrhythmias, and a history of cardiac pathology, were excluded from the current study. Contrary to the literature, at the end of the current study, no changes associated with ZA administration were observed in the electrolyte levels. However, at the end of the first day, there was one patient who had a right bundle branch block that resolved on its own by the end of the first day.

Recent studies suggest that temporary and moderate reductions of Ca^{2+} levels may lead to AF and VA.[16,30,34,35] In the current study, to avoid these arguments, patients were supplemented with Ca^{2+} preparations before ZA administration and we did not observe any electrolyte imbalance that would be the possible cause of arrhythmia.

We observed mild anemia in 18.2% of patients after ZA administration and the rest had average Hb levels of 12.7±1.1 g/dL.

Normal blood concentrations of many medications may not lead to arrhythmias but during the few days following their administration, when they reach lower concentrations in the blood, they may lead to arrhythmia.[34] Also, in some cases, patients administered ZA have developed a very early side effect profile. One study found that a month after ZA administration, very low concentrations of ZA molecules in the blood might lead to AF.[30] However, in the current study, the ZA-associated AF risk was observed.

Many medications, whether used in the pharmaceutical treatment of OP or not, prolong QT intervals and may lead to arrhythmias. Besides these medications, drugs that lead to enzymatic reactions, such as the inhibition of CYP3A4 isoenzyme, may prolong QT intervals and may lead to arrhythmias. Also, poly medication, which is controlled by the

Table 4. Comparison of changes between the corrected QT dispersion, based on 50 milliseconds cut-off value, before and 11 days after zoledronic acid administration

Cut-off (msec)	Before ZA administration		11 Days after ZA administration		
	Frequency	%	Frequency	%	*p*
≤50.00 (normal)	33	100.0	24	72.7	
>50.00 (abnormal)	0	0.0	9	27.3	0.004
Total	33	100.0	33	100.0	

ZA: Zoledronic acid; * Mc Nemar chi-squared test.

ventricular potassium flux and prolongs QT interval duration, can cause significant increases in the risk of arrhythmia.[36] Even though OP patients treated with poly medication were excluded from the study, ECG findings of the patients showed a variance in QT intervals.

QT intervals, which have always been a measure of the time required for ventricular depolarization and repolarization to occur, adapt to changes in heart rate. Therefore, QTc values have been based on different heart rates.[23,24] QTc has significant importance in the prognosis of total and cardiovascular mortality.[31]

During the first hour following ZA administration, ECG data was normal. However, on the 11th day following ZA administration, QTcd values were significantly higher. As a result of this finding, we think that arrhythmia would be possible with the ZA administration.

In conclusion, because factors such as electrolyte imbalance, including hypocalcaemia, may increase the predisposition to AF, electrolyte imbalance during treatment of OP with all types of BPs should be monitored closely. It should not be forgotten that while treating patients with OP using mostly ZA, there is a significant difference between the values for Pd and RR intervals before and after ZA administration. Another point to remember is the change observed in QTcd values, which is an indicator of ventricular arrhythmia. The observed changes in ECG parameters were evident when the electrolyte levels were stable. When patients with OP are assigned to be treated with BPs, administering ZA after eliminating any electrolyte imbalance is very important. It is also safer to administer ZA when the patient's Hb and vitamin D levels are within normal range. Even if patients do not have cardiac pathologies, while planning to use ZA administration for OP treatment in elderly patients, cardiac parameters should be evaluated.

Declaration of conflicting interests

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