

## Effects of cinacalcet treatment on QT interval in hemodialysis patients

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### ABSTRACT

**Objective:** Cinacalcet is a calcimimetic drug that acts via calcium-sensing receptors (CaSRs) and increases the sensitivity of CaSRs on the parathyroid gland; thus, it lowers calcium and phosphorus levels as well as parathormone levels. Prolongation of the QT interval is recognized as a risk factor for the development of ventricular arrhythmias and sudden death. Patients with end-stage renal disease (ESRD) are sensitive for QT prolongation and torsade de pointes more than the normal population. In this study, we aimed to evaluate the effects of cinacalcet on the electrocardiogram (ECG), particularly changes in the QT interval, in patients with ESRD.

**Methods:** Thirty-seven patients (21 males and 16 females) undergoing maintenance hemodialysis for at least 12 months were included in this retrospective study. Patients receiving cardioactive and antiarrhythmic drugs and those having a history of any cardiac or cerebrovascular events, active malignancy, and infections were excluded. Baseline ECG measurements of patients were performed over the newest ECG measurements that were obtained within 1 month before initiating the cinacalcet treatment, and the ECG measurements of patients after the cinacalcet treatment were performed according to the most recent ECG that was taken within the last 1 week in the clinic. We recorded the heart rate and QT values of patients before and after treatment and then calculated the corrected QT values (QTc). The Statistical Package for the Social Sciences (SPSS) ver. 21.0 was used for statistical analysis.

**Results:** The mean age of patients was 52.24±14.49 years. Prolongation of QTc was statistically significant compared with the baseline QTc value (baseline: 396.62±42.04 msec; after treatment: 404.97±43.47 msec; p=0.031). We found a positive correlation between the prolongation of QTc and treatment dose of cinacalcet (p<0.005, r=0.560).

**Conclusion:** Clinicians should be very careful for life-threatening cardiac side effects while increasing the dose of cinacalcet treatment in hemodialysis patients who have a borderline or prolonged QTc interval. (*Anatol J Cardiol* 2016; 16: 520-3)

**Keywords:** calcimimetics, cinacalcet, QT interval, Torsade de Pointes

### Introduction

Cinacalcet is a calcimimetic agent which increases the sensitivity of the calcium-sensing receptor (CaSR) to extracellular calcium (Ca), and this leads to the reduced release of parathormone (PTH) (1, 2). CaSR is a member of the subfamily C of G protein-coupled receptors (GPCRs) (3). The activation of the receptor by an increase in extracellular Ca initiates a signal transduction through pathways that had been demonstrated previously to be linked directly to a decrease in PTH release from parathyroid cells (4, 5). As a calcimimetic drug, cinacalcet is used to lower PTH, serum Ca, and serum phosphorus levels; hence, it prevents progressive bone disease and comorbid situations associated with secondary hyperparathyroidism and mineral metabolism disorders. The mechanism of action is through CaSRs. It increases the sensitiv-

ity of CaSRs on the parathyroid gland and as a result it lowers Ca and phosphorus levels as well as PTH levels (6). CaSR belongs to a member of GPCR, and it has been identified in many tissues such as the thyroid, kidney, bone, gastrointestinal tract, and heart (7–11). As allosteric modulators of these receptors, calcimimetics and therefore cinacalcet may have many effects beyond lowering of PTH levels. It is currently not well-known whether all of these effects of calcimimetics are due to lowering PTH levels or they have direct effects on target tissues such as the heart. As an essential cation, Ca regulates and maintains many cell functions, one of which is the cardiac heart cells. In both cardiac and skeletal muscles, cross bridges are activated by increasing the intracellular free Ca level that regulates the troponin-tropomyosin system; thus, changes in serum Ca levels may alter the cardiac contractility and therefore result in changes in the electrocardiogram (ECG) (12). The QT inter-

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val is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. torsade de pointes is a form of polymorphic ventricular tachycardia occurring in a setting of prolonged QT interval on the surface ECG. It has been reported that QTc interval prolongation and torsade de pointes is associated with end-stage renal disease (ESRD) and that they can be a cause of sudden death in ESRD (13, 14). Hypocalcaemia influences cardiac repolarization by inducing prolongation of the QT interval, which represents the electrical depolarization and repolarization of the ventricles. Prolongation of the QT interval is recognized as a risk factor for the development of ventricular arrhythmias and sudden death. In this study, we aimed to evaluate the effects of cinacalcet on Ca and ECG as a widely used calcimimetic agent in patients with renal failure.

## Methods

### Patient selection

Our study was a retrospective study, and 37 adult uremic patients undergoing maintenance hemodialysis for at least 12 months were enrolled for this study. Patients receiving cardioactive drugs such as beta blockers, alpha blockers, or any antiarrhythmic medication; those with a history of cerebrovascular disease, coronary artery disease, left ventricular hypertrophy, cardiac valve disease, and bundle branch block, those having cinacalcet treatment duration of less than 6 months, those receiving medications that may prolong the QT interval, those with heart failure, active infection, or malignancy, and those with dilated cardiomyopathy were excluded. Patients were eligible if they were free from any acute cardiovascular disease or arrhythmias. Hemodialysis was performed in three 4-h sessions per week, and all patients were dialyzed with a minimum of 1.25 mmol/L Ca dialysate. The adequacy of dialysis was assessed by Kt/V urea, using the urea kinetic model of Gotch (15); patients with a Kt/V value higher than 1.2 were selected for the study. Data including age, gender, duration of cinacalcet treatment, dose of cinacalcet, and corrected Ca and intact parathormone (iPTH) levels before and after treatment were reviewed and recorded. The baseline ECG measurements of patients were performed over the newest ECG measurements that were obtained within 1 month before initiating the cinacalcet treatment, and the ECG measurements of patients after the cinacalcet treatment were performed according to the most recent ECG that was taken within the last 1 week in the clinic. ECG measurements were recorded with a standard resting 12-lead ECG (Nihon Kohden EXG-9022, Nihon Kohden Corporation, Tokyo, Japan) at a paper speed of 25 mm/s after more than 5 min of rest. The space between the start of the Q wave and the end of the T wave was defined as the QT interval, and the interval from the peak of one QRS complex to the peak of the next QRS complex was defined as the R-R interval (Fig. 1). We recorded the heart rate and QT values of patients before and after treatment and then calculated the corrected QT values (QTc) according to Bazett's formula (QTc interval = QT interval/square root of R-R interval).

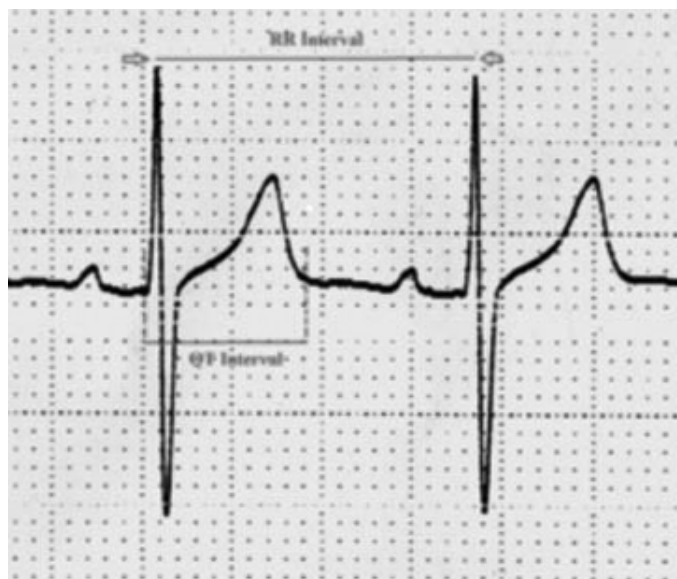


Figure 1. Definition of the QT interval and RR interval

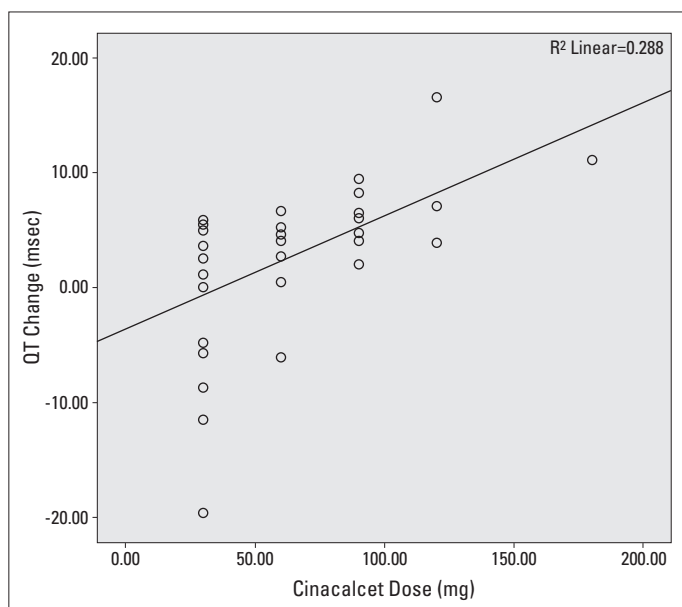
All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 21.0, and all the data were expressed as the mean  $\pm$  standard deviation (SD). A p value of less than 0.05 was considered significant. Categorical variables were compared using the Mann–Whitney U test or Kruskal–Wallis test. Shapiro–Wilk's test was used for the determination of normal distribution. Wilcoxon's test was used for the comparison of parameters before and after treatment. Spearman's correlation analysis was used for the comparison of data.

## Results

The mean age of the subjects was  $52.24 \pm 14.49$  years. The mean corrected serum Ca levels before and after treatment were as follows: baseline  $9.22 \pm 0.85$  mg/dL and after treatment  $9.08 \pm 0.65$  mg/dL. The mean serum iPTH levels before and after treatment were as follows: baseline  $1405 \pm 590$  pg/mL and after treatment  $1186 \pm 564$  pg/mL. The mean duration of cinacalcet treatment was  $13.45 \pm 6.52$  months, and the mean Kt/V value of patients was  $1.47 \pm 0.20$ . The decrease in serum Ca levels before and after treatment was not statistically significant ( $p=0.182$ ) but serum iPTH levels decreased significantly after treatment ( $p=0.031$ ). Prolongation of QTc was statistically significant compared with the baseline QTc value (baseline:  $396.62 \pm 42.04$  msec; after treatment:  $404.97 \pm 43.47$  msec;  $p=0.031$ ). The division of patients according to the cinacalcet dose is shown in Table 1. We

Table 1. Distribution of patients according to the dose of cinacalcet

Dose of Cinacalcet (mg)	Number of patients
30	17
60	9
90	7
>120	4

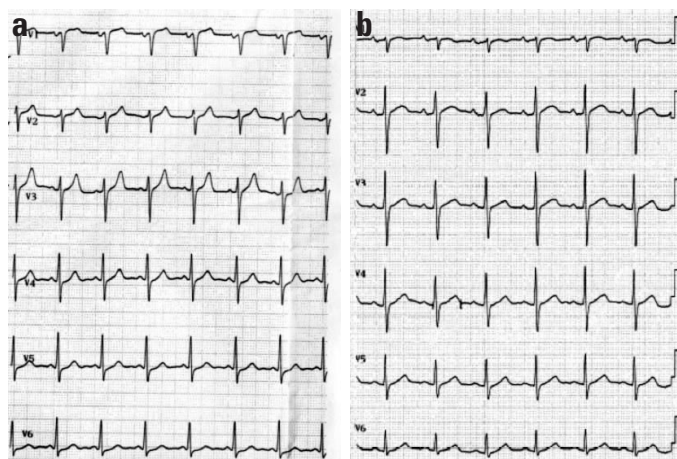


**Figure 2. Correlation between the cinacalcet dose and changes on the QT interval. The X-axis shows the cinacalcet dose of patients, while the Y-axis shows the changes in msec according to the baseline QT interval (SPSS 21.0 for Windows)**

found a positive correlation between the prolongation of QTc and treatment dose of cinacalcet ( $r=0.560$ ,  $p<0.005$ ), (Fig. 2). There was no correlation between the duration of cinacalcet treatment and changes in serum Ca levels and QTc ( $r=0.253$ ,  $p=0.131$  and  $r=0.188$ ,  $p=0.265$ , respectively). There was a statistically significant correlation between the decrease in iPTH levels and the dose of cinacalcet treatment ( $r=0.366$ ,  $p=0.02$ ). There was also a statistically significant correlation between the decrease in iPTH levels and the prolongation of QTc ( $r=0.327$ ,  $p=0.048$ ). There was no arrhythmia during the period of cinacalcet treatment, and there was no statistically significant difference between male and female subjects according to the QT change before and after treatment with cinacalcet ( $p=0.057$ ).

## Discussion

In our study, both baseline and after treatment QTc values were in the normal range. However, interestingly, with an increased dose of cinacalcet treatment, the QTc interval of patients was significantly prolonged. Furthermore, this prolongation was not related with both baseline and after treatment levels of Ca of hemodialysis patients. This was important because previous studies such as those of Borrego-Utiel et al. (16) reported a QTc prolongation related with baseline Ca levels and hypocalcaemia. Figure 3 shows an ECG sample of a prolonged QT after cinacalcet treatment. In the setting of chronic kidney disease, long-term treatment with cinacalcet has proven to be efficient in controlling PTH levels and subsequently Ca and P levels (6). CaSR was originally cloned from parathyroid chief cells in 1993; however, the existence of CaSR has also been subsequently identified in the thyroid, kidney, bone, and gastrointestinal tract



**Figure 3. The ECG samples of a patient before (a) and after (b) cinacalcet treatment**

tissues, which participate in the regulation of systemic Ca homeostasis (8–11, 17). In 2003, the expression of CaSR in cardiac tissues was shown and also revealed that the activation of CaSR leads to intracellular Ca release via G protein-phospholipase C-inositol, 4,5-triphosphate pathway (18). It has been shown that calcimimetics have some beneficial effects such as lowering the blood pressure and improving cardiac morphology, but it is currently unknown that all of these effects of calcimimetics on the cardiovascular system or other target tissues are a result of lowering PTH levels or that calcimimetics have some direct effects on the heart and other tissues (19, 20).

Our study also showed that cinacalcet was really effective for reducing increased iPTH levels, particularly in higher doses as an expected effect from itself. Therefore, we found a positive correlation between the decrease in iPTH levels and prolongation of QTc. The decrease in iPTH levels without causing hypocalcemia a simultaneous prolongation of QTc in hemodialysis patients led us to hypothesize that cinacalcet, particularly in higher doses, may cause some dose-related but Ca-independent effects outside the parathyroid gland such as the heart. These results were important because hemodialysis patients were already sensitive to the prolongation of QTc and torsade de pointes. Recently, increasing the use of cinacalcet for the treatment of secondary hyperparathyroidism in dialysis patients may increase the risk for torsade de pointes and sudden cardiac death, particularly in high doses or in patients who have an already prolonged QTc interval.

## Study limitations

Our study has some limitations. First, this study was a retrospective study. It would be better to design prospective studies to evaluate the cardiac effects of cinacalcet. Second, the number of patients in our study was not sufficient to make a definitive conclusion for the cardiac effects of cinacalcet; however, the results of this study were important. Third, because this is a retrospective study, we aimed to evaluate the effects of cinacalcet

in hemodialysis patients; therefore, we did not have a control group, and thus, we were unable to define a threshold dose for the development of QT prolongation that could be attributable to cinacalcet treatment. Finally, we did not evaluate the intra- and inter-observer variability of QT duration measurements.

## Conclusion

In conclusion, we found that increasing the dose of cinacalcet treatment was related with the significant prolongation of the QTc interval of hemodialysis patients according to the baseline values. Clinicians should be extremely careful about life-threatening cardiac side effects while increasing the dose of cinacalcet treatment, particularly in hemodialysis patients who have a borderline or prolonged QTc interval. We thought that sufficient consideration should be given to ECG and QTc measurements in daily practice in dialysis clinics, particularly in patients receiving cinacalcet treatment.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

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