A) BRIEF PAPERS ON RESEARCH AND CLINICAL EXPERIMENTS

Cinacalcet may prolong the QT interval in patients on haemodialysis with secondary hyperparathyroidism

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To the Editor:

Cinacalcet is a calcimimetic drug widely used in the treatment of primary and secondary hyperparathyroidism. It can effectively reduce the levels of parathyroid hormone (PTH) and phosphorus in patients with secondary hyperparathyroidism by acting on the calcium-sensing receptor, at the same time causing a significant reduction in serum calcium levels. Calcium is a cation with a fundamental role in cardiac function, influencing the contraction of the myocardial cell, cardiac cycle regulation and the maintenance of said cell membrane's potential thanks to the potassium-calcium channels. Changes in serum calcium levels cause changes in the electrocardiogram (ECG), mainly in the ST and QT segments. Hypocalcaemia influences cardiac repolarisation by inducing a significant prolongation of the QT interval, which is recognised as a risk factor for the development of ventricular arrhythmias (*torsades de pointes*) and sudden death.[1,2] In epidemiological studies of unselected population, the existence of low serum calcium levels has been associated with longer QT[2] intervals. In patients with hypocalcaemia secondary to hypoparathyroidism or after the use of bisphosphonates, the QT interval may be prolonged clearly and significantly.[3] When patients with hypocalcaemia undergo treatment with calcium supplements and vitamin D metabolites, there is a progressive shortening of the QT although initially the QT value was not pathological.[4] In patients on haemodialysis, the QT interval is greater than in the general population and is also inversely related to serum calcium levels.[5] When performing haemodialysis with low calcium dialysate, there is QT prolongation and increased QT interval dispersion,[6] which is also recognised as a risk factor of severe arrhythmia.[1]

The effect of the decrease in serum calcium on QT interval after cinacalcet in haemodialysis patients has not been studied. Therefore, we decided to analyse whether ECG changes can be detected after treatment with cinacalcet. We selected patients who had been treated with cinacalcet for at least 6 months and with ECG before receiving it and after 3-6 months of treatment. We recorded heart rate, QT and RR intervals and calculated corrected QT values (QTc with Bazett's formula). The study included 33 patients of 60±15 years of age and 70±56 months on dialysis. After cinacalcet administration, intact PTH decreased significantly (baseline 647±329pg/ml; 6 months 466±361pg/ml, *P*=.001). Serum calcium decreased significantly in the first 3 months (baseline 9.7±0.8mg/dl, 3 months 8.9±0.9mg/dl, *p*<.001) and then did not undergo major changes. At baseline, 2.7% had hypocalcaemia (Ca<8.5 mg/dl), whereas at 3 months this figure increased to 31.5% and then stabilised at between 17.6% and 22.5%. Heart rate was unchanged, while the QT interval was significantly prolonged (baseline 366±39ms, final 394±56ms, *P*=.012). QTc was also prolonged, although it did not become significant (baseline 409±37ms, final 425±42ms). The RR interval was not significantly prolonged (baseline 813±164ms, final 863±139ms). Before cinacalcet 3 (9.1%) patients had a QTc>450ms and on final ECG, there were 7 patients (21.2%). The prolongation of QTc did not correlate with age, cinacalcet dose, serum potassium, bicarbonate or PTH baseline or final levels. However, we observed that QT prolongation correlated with baseline serum calcium (r=0.35, *P*=.045), and as such, patients with higher baseline calcium showed higher prolongation of QT. Dividing the population according to tertiles of baseline serum calcium, we note that QT was further prolonged in patients with calcium from 9.4 to 9.9mg/dl (baseline QT 359±33 vs. final 397±46ms, *P*=.023) and calcium>9.9mg/dl (baseline QT 358±47 vs. final 410±65ms, *P*=.065).

The QT interval and QT dispersion in haemodialysis are higher than in the general population[7,8] and shorten toward normality after renal transplantation.[8] A prolongation of the QTc>440ms was detected in 33.8% of patients before dialysis and after dialysis it may rise to 45.6%.[5] The QT is very clearly prolonged after dialysis in those who start from higher serum calcium levels and in those with higher decreases in their figures,[5] especially if low calcium bath is used.[6] QT prolongation is related to the presence of diastolic dysfunction[9] and along with QT dispersion, they are risk factors for mortality in patients with peripheral vascular disease, ischaemic heart disease and dilated/hypertrophic cardiomyopathy.[9] The development of severe hypocalcaemia in haemodialysis patients may create an added risk of developing cardiac events in patients with severe ventricular hypertrophy or baseline cardiomyopathy, in whom there may already be a prolongation of QT, or in patients with effective medication for this interval.

Our observation is important for the EVOLVE study currently being carried out.[10] This study was specifically designed to analyse whether or not cinacalcet may benefit the survival of haemodialysis patients, based on the idea that it may reduce coronary and vascular calcification, lowering cardiovascular mortality. If cinacalcet induced hypocalcaemia provoked a QT prolongation in high enough amounts,

it could trigger severe arrhythmias which would limit the potential benefit as regards the survival of haemodialysis patients. In fact, there are some studies that describe hypocalcaemia as a risk factor for increased mortality in patients on haemodialysis.[11]

We believe that our observation of a potential QT prolongation in patients on haemodialysis treated for secondary hyperparathyroidism with cinacalcet means that special vigilance is required in patients with high calcium or when there is significant hypocalcaemia. It would be advisable to carry out an ECG and check if there is a prolongation of QT beyond the limits that are considered dangerous due to the appearance of severe ventricular arrhythmias. This should be taken into account especially in patients receiving antiarrhythmic medication that may prolong QT or in patients with ischaemic heart disease or previous dilated cardiomyopathy. We also recommend reviewing data from prospective studies carried out with cincalcet or proposing that future prospective studies be accompanied by the implementation of an ECG to check the clinical significance of the data presented herein.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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B) BRIEF CASE REPORTS

Effectiveness of early haemodialysis in cefepime-induced neurotoxicity

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To the Editor:

Cefepime is a fourth-generation cephalosporin, active against gram-positive organisms such as *Staphylococcus aureus*, and gram-negative organisms such as *Pseudomonas aeruginosa*.[1,2]

The kidney is the primary elimination route, with over 80% of cefepime being recovered with no change in the urine of patients with normal renal function.

The elimination half-life is 2-2.5 hours. It has low plasma protein binding, ap-