Cinacalcet in peritoneal dialysis patients: one-center experience

Cinacalcet em diálise peritoneal: a experiência de um centro

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Abstract

Introduction: Secondary hyperparathyroidism is the target of several therapeutic strategies, including the use of cinacalcet. Most studies were done only in hemodialysis patients, with few data from peritoneal dialysis patients. **Objective:** The aim of our work was to evaluate the effectiveness of cinacalcet in secondary hyperparathyroidism in a one-center peritoneal dialysis patients. **Methods:** A retrospective study was performed in 27 peritoneal dialysis patients with moderate to severe secondary hyperparathyroidism (PTHi > 500 pg/mL with normal or elevated serum calcium levels) treated with cinacalcet. Demographic, clinical and laboratory parameters at the beginning of cinacalcet therapy, second, fourth, sixth months after and at the time it was finished were analyzed. **Results:** Patients were under peritoneal dialysis at 30.99 ± 16.58 months and were treated with cinacalcet for 15.6 ± 13.4 months; 21 (77.8%) patients showed adverse gastrointestinal effects; PTHi levels at the beginning of cinacalcet therapy were 1145 ± 449 pg/mL. The last PTHi levels under cinacalcet therapy was 1131 ± 642 pg/mL. PTHi reduction was statistically significant at 2 months after the beginning of cinacalcet (p = 0.007) but not in the following evaluations. **Conclusion:** It is necessary the development of new forms of cinacalcet presentation, in order to avoid gastrointestinal effects adverse factors and to improve therapeutic adherence.

Keywords: Calcimimetic agents; hyperparathyroidism, secondary; kidney failure, chronic; peritoneal dialysis.

Resumo

Introdução: O hiperparatiroidismo secundário é alvo de várias estratégias terapêuticas, incluindo a utilização de cinacalcet, sendo escassos os resultados referentes aos doentes em diálise peritoneal. **Objetivo:** Propusemo-nos a avaliar a eficácia da terapêutica com cinacalcet no tratamento dos doentes com hiperparatiroidismo secundário numa unidade portuguesa de diálise peritoneal. **Métodos:** Estudo retrospectivo que incluiu 27 doentes em diálise peritoneal com hiperparatiroidismo secundário moderado a grave (PTHi > 500 pg/mL) tratados com cinacalcet. Foram analisados os dados demográficos, clínicos e laboratoriais à data de início da terapêutica, ao segundo, quarto e sexto mês e à data do fim do estudo ou da suspensão do mesmo. **Resultados:** Os doentes estavam em diálise peritoneal há 30,99 ± 16,58 meses e foram tratados com cinacalcet durante 15,6 ± 13,4 meses; 21 (77,8%) doentes apresentaram efeitos adversos gastrointestinais. Os valores de PTHi no início da terapêutica com cinacalcet eram 1145 ± 449 pg/mL. Os últimos valores de PTHi foram 1,131 ± 642 pg/mL. A redução da PTHi foi estatisticamente significativa aos 2 meses após o início do cinacalcet (p = 0,007), mas não nas avaliações subsequentes. **Conclusão:** Torna-se necessário o desenvolvimento de novas formas de apresentação do cinacalcet, de modo a evitar os efeitos adversos gastrointestinais e melhorar a adesão terapêutica.

Palavras-chave: Calcimiméticos; diálise peritoneal; falência renal crônica; hiperparatireoidismo secundário.

Introduction

Mineral bone disease (MBD) has been studied in patients with chronic kidney disease (CKD), including in the patients who are under any dialysis technique. It has been proved that CKD-MBD is responsible for the clinical progress, complications under technique and patient survival.[1] The secondary hyperparathyroidism (SHPT) is the target of several therapeutic strategies, including the use of cinacalcet, which may improve some CKD-MBD outcomes.[2,3] SHPT is very common in dialysis patients and is characterized by elevated parathyroid hormone (PTH) and disordered mineral metabolism. The calcimimetic cinacalcet was approved by the US Food and Drug Administration in 2004 and by European Committee for Medical Products for Human Use in 2005 to treat SHPT in patients on dialysis.[4]

Cinacalcet acts directly upon the parathyroid cell calcium-sensing receptor (CaR). Upon binding CaR, cinacalcet allosterically increases its sensitivity to extracellular calcium thus suppressing PTH secretion without increasing serum calcium and phosphate levels.[5,6] Until 2008, most of the published studies of cinacalcet in dialysis patients, included a small number of peritoneal dialysis (PD) patients.[7,8] A Spanish one-center observational prospective study of 18 patients under PD published in 2008, proved that the use of cinacalcet in PD patients with SHPT resistant to conventional treatment has resulted effective and safe and has improved compliance objectives of the guidelines.[9] This results were corroborated in 2012, in a Spanish multicenter observational prospective study of 54 PD patients.[10] The incidence of CKD-MBD is different in PD and HD patients.[11] So, it is expectable that the treatment and the results could differ in both groups. The aim of the present study was to evaluate the effectiveness of cinacalcet in SHPT in a one-center peritoneal dialysis patients.

Methods

This is a retrospective study performed at a single PD Unit based on the study of a cohort of 27 patients with moderate to severe SHPT (PTHi > 500 pg/mL with normal or elevated serum calcium levels) who were treated with cinacalcet. Cinacalcet was started due to the lack of response with conventional treatment: diet, phosphate binders and vitamin D or inability to treat with vitamin D due to hyperphosphatemia (> 5.5 mg/dL) or hypercalcemia (> 10.5 mg/dL).

Demographic, clinical and laboratory parameters at the beginning of cinacalcet therapy, second, fourth, sixth months after and at the time it was finished were registered. In patients who were still under cinacalcet therapy, we analyze the last laboratorial available results, the time under cinacalcet therapy, maximum tolerated doses, effectiveness and safety, including the adverse effects. Measurements of calcium were corrected for serum albumin. All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) 14.0 software (SPSS, Inc., Chicago, IL, USA). Categorical variables were described as numbers or percentage of relative frequencies and quantitative variables as mean ± standard deviation (SD) for continuous normally distributed variables. Cox regression was used to compare survival rates. Differences between clinical data were assessed by Student's t-test for paired samples for normal variables, paired Wilcoxon test for continuous data with non-normal distribution. A p value of < 0.05 was considered to be statistically significant.

Results

Mean age was 46.3 ± 15.7 years; 15 (55.6%) patients were men, six (22.2%) patients had diabetes and the body mass index (BMI) at the beginning of PD was 26.4 ± 5.2 Kg/m^2. Patients were under PD at 31 ± 16.6 months; all 27 patients were treated with cinacalcet for 15.6 ± 13.4 months. The minimum doses was 15 mg/day and the maximum doses was 90 mg/day (mean 45 mg/day).

In 21 (77.8%) patients was not possible to increase cinacalcet over 45 mg/day due to adverse gastrointestinal effects (nausea and/or dyspepsia); five patients drop out the program under cinacalcet therapy (four patients started HD and one patient received a kidney allograft); 63% of patients were treated with PD solutions with low calcium levels (1.25 mmol/L) and 37% with DP solutions containing calcium at 1.75 mmol/L; 25 (92.6%) patients were under treatment with vitamin D analogs and phosphorus binders (sevelamer range 1600 mg to 4800 mg/day); two (7.4%) patients were unable to start vitamin D due to hypercalcemia (Table 1). The laboratorial levels at the beginning of cinacalcet therapy were: PTHi: 1145

Table 1 Demographic, clinical and laboratory characteristics of patients treated with cinacalcet

	Cinacalcet therapy (n = 27)
Age (years)	46.3 ± 15.7
Gender – male (n/%)	15 (55.6%)
Diabetes (n/%)	6 (22.2%)
BMI (Kg/m^2)	26.4 ± 5.2
Time under PD (months)	31 ± 16.6
Time under cinacalcet (months)	15.6 ± 13.4
Cinacalcet doses (mg/day)	45 (15-90)
Adverse GI effects (n/%)	21 (77.8%)
Patients treated with vitamin D analogs/phosphorus binders (n/%)	25 (92.6%)

BMI: body mass index; PD: peritoneal dialysis; GI: gastrointestinal

± 450 pg/mL; calcium: 9.2 ± 0.9 mg/dL; phosphorus: 5.3 ± 0.7 mg/dL and nPCR: 1.1 ± 0.3 g/kg/day. PTHi, calcium and phosphorus levels at the second, fourth and sixth months after starting cinacalcet, were, respectively; 926 ± 397 pg/mL; 8.8 ± 1 mg/dL and 5.1 ± 1 mg/dL in the second month; 1028 ± 576 pg/mL; 8.9 ± 0.9 mg/dL and 5.8 ± 0.9 mg/dL in the four month and 1011±553 pg/mL, 8.9 ± 0.7 mg/dL and 5.6 ± 1.1 mg/dL in the sixth month.

The last laboratorial follow up under cinacalcet therapy was: PTHi: 1132 ± 643 pg/mL; calcium: 9.2 ± 0.9 mg/dL (two patients had calcium levels < 8 mg/dL); phosphorus: 5.9 ±1 mg/dL and nPCR: 1 ± 0.2 g/Kg/day (Figure 1). PTH reduction was statistically significant at 2 months after the beginning of cinacalcet (p = 0.007) but not in the following evaluations. Type of PD solution (1.25 x Ca 1.75 mmol/l) was not a predictor of changes in the values of calcemia, phosphatemia or iPTH (p value without statistical significance). At the last follow up, 21 (77.8%) patients had PTHi levels higher than 600 pg/mL despite cinacalcet therapy at maximum tolerated doses. The phosphorus levels were increasing during PD (p = 0.03) but nPCR was similar to the value at the beginning of PD.

Discussion

Some of the recent European studies found similar prevalence of SHPT in incident PD and HD patients, with calcium and phosphorus levels being very similar in both techniques.[1] However, PD patients have some differences from HD patients in cinacalcet handling.

As a Spanish study showed,[9] hypocalcemia (calcium < 8 mg/dL) was rarely found in our patients (two patients) and none was symptomatic. Continuous presence of intra-abdominal fluid with adequate levels of calcium improve this imbalance and protect patients from hypocalcemia. Our major difference from the other studies of cinacalcet in PD patients[9,10] was the impossibility to improve the biochemical control of SHPT in PD patients after the second month of therapy. We prescribed cinacalcet in low doses (mean 45 mg/day) and only two patients tolerated doses of 90 mg/day. The dose titration of cinacalcet was done more gradually than the recommendation guidelines, in which the dose was increased every month if they had not reached goals.[12] We assume that the lack of response to cinacalcet was due to the adverse gastrointestinal effects which made impossible the prescription of higher doses of cinacalcet. PD patients are predisposed to adverse gastrointestinal effects because of the fullness and increased abdominal pressure associated with PD.

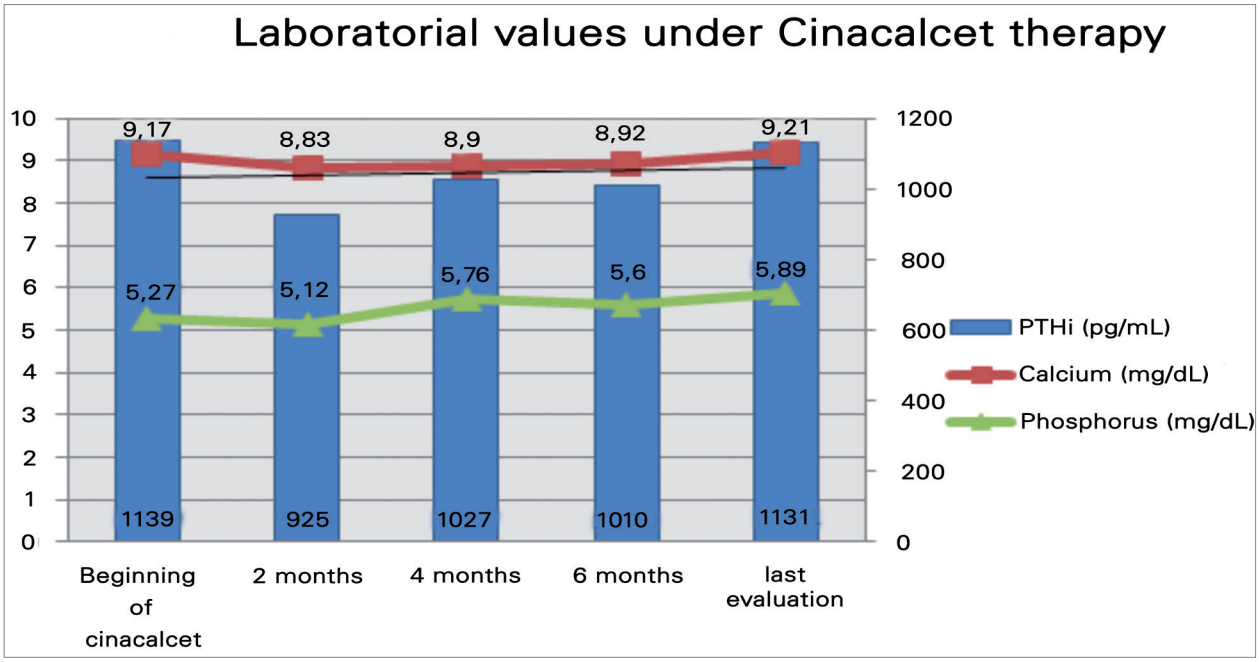
Calcium receptors in gastrointestinal tract are responsible for the gastrointestinal effects, such as nausea and dyspepsia.[13] In our series, 21 (77.8%) patients showed adverse gastrointestinal effects with cinacalcet > 30 mg/day. An eventual benefit of this therapy at higher doses in SHPT was impossible to evaluate.

However, in other studies,[9,10] cinacalcet was well tolerated, considering that dyspepsia was recorded only in 17%[9] and 7.4%[10] of patients. In the first report,[9] discontinuation of cinacalcet administration was not required in any patient; in the second study,[10] all patients with digestive intolerance reduced or discontinued cinacalcet, with the appearance of side effects being similar or even lower than that reported for HD.[14]

Additionally, in our report 92.6% of patients were treated with phosphate binders, which, alone, could lead to gastric intolerance. Probably the diet, the administration of cinacalcet with or without food and the confounding factor of phosphate binders gastrointestinal effects', could have a role in the high rate of gastric intolerance symptoms in our serie.

New forms of cinacalcet presentation, in order to avoid gastrointestinal adverse factors and improve therapeutic adherence, could be effective to treat this patients.

Figure 1. Laboratorial values under cinacalcet therapy at the beginning of cinacalcet therapy, 2nd, 4th, 6th months and at the last evaluation.



Conclusion

Cinacalcet was a safe but not effective therapy in moderate to severe SHPT in PD patients. The gastrointestinal adverse factors made impossible the prescription of higher doses of cinacalcet and an eventual benefit of this therapy at higher doses in SHPT was impossible to evaluate. It is necessary to develop new forms of cinacalcet presentation, in order to avoid GI adverse factors and to improve therapeutic adherence.

Conflict of interest

No conflict of interest have been declared.

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