Effectiveness and safety of a 6-month treatment with paricalcitol in patients on hemodialysis with secondary hyperparathyroidism

Eficácia e segurança do tratamento de 6 meses com paricalcitol em pacientes em hemodiálise com hiperparatiroidismo secundário

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ABSTRACT

Introduction: The mineral bone disorder, particularly secondary hyperparathyroidism, in chronic kidney disease (CKD) has a systemic impact affecting not only bone metabolism. Therefore its correction is important to prevent cardiovascular, inflammatory and immune diseases. **Objective:** To assess the effectiveness and safety of intravenous paricalcitol administered over a 6 month period for the treatment of secondary hyperparathyroidism (SHPT) in patients undergoing conventional hemodialysis, with close follow-up of treatment response. **Methods:** A phase 4 clinical trial was performed comparing clinical and laboratory data before and after 6 months of treatment. SHPT patients undergoing hemodialysis who were naïve to vitamin D metabolites or had failed to current therapy were included. Clinical and laboratory characteristics were analyzed. Efficacy analyses were based on intact parathyroid hormone (iPTH) levels and were performed using data from patients who completed 6 months of treatment. **Results:** Nineteen of the 26 patients enrolled completed 6 months of treatment. All patients exhibited reduced baseline iPTH levels (mean reduction, 371.8 pg/mL; 95% CI, 273.3-470.2 pg/mL]; 17 patients (89.5%) had reductions exceeding 30%. Twelve patients (63%) achieved therapeutic success (defined as iPTH serum levels 150-300 pg/mL), with a median time of 2 months from the beginning of treatment. All reported episodes of hypercalcemia (n = 2) and hyperphosphatemia (n = 34) were asymptomatic. No major therapy-related serious AEs were reported. **Conclusion:** Paricalcitol was safely administered and was associated with significant decreases in iPTH levels over the study period.

Keywords: hypercalcemia; hyperparathyroidism, secondary; hyperphosphatemia; dialysis.

RESUMO

Introdução: A doença metabólica óssea, em particular o hiperparatireoidismo secundário, na doença renal crônica (DRC) tem um impacto sistêmico que afeta nem só o metabolismo ósseo. Por tanto, sua correção é importante para prevenir as doenças do sistema imunitário, inflamatório e cardiovascular. **Objetivo:** Avaliar a eficácia e a segurança do paricalcitol intravenoso administrado durante um período de 6 meses no tratamento do hiperparatireoidismo secundário (SHPT) em pacientes submetidos a hemodiálise convencional, com acompanhamento de perto da resposta do tratamento. **Métodos:** Realizou-se um ensaio clínico de fase 4 que comparava os dados clínicos com os dados do laboratório antes e depois dos 6 meses de tratamento. Incluíram-se os pacientes SHPT em hemodiálise sem experiência com os metabólitos da vitamina D ou que fracassaram com a terapia em uso. Analisaram-se as características clínicas e de laboratório. As análises de eficácia se basearam nos níveis do hormônio da paratireóide intacto (iPTH) e foram realizadas usando dados dos pacientes que completaram os 6 meses de tratamento. **Resultados:** Dezenove dos 26 pacientes registrados completaram os 6 meses de tratamento. Todos os pacientes mostraram níveis de referência iPTH reduzidos (redução média, 371,8 pg/mL; 95% CI, 273,3-470.2 pg/mL]; 17 pacientes (89,5%) tiveram reduções superiores a 30%. Doze pacientes (63%) conseguiram o sucesso terapêutico (definido como níveis de soros iPTH de 150-300 pg/mL), com um tempo médio de 2 meses a partir do início do tratamento. Todos os episódios de hipercalcemia (n = 2) e de hiperfosfatemia (n = 34) reportados foram assintomáticos. Não se informaram AEs graves importantes relacionados à terapia. **Conclusão:** O paricalcitol foi administrado de forma segura e se associou às reduções significativas nos níveis de iPTH durante o período do estudo.

Palavras-chave: hiperparatireoidismo secundário; hipercalcemia; hiperfosfatemia; diálise.

Introduction

Secondary hyperparathyroidism (SHPT) continues to be a frequent complication in patients with chronic kidney disease (CKD), particularly in patients receiving dialysis. As the severity of CKD progresses, there is evidence of irreversible molecular changes in the parathyroid gland that requires early and appropriate treatment.[1,2] During the past few years, increasing emphasis has been placed not only on the need for prompt treatment, but also on ensuring a rapid response to treatment: patients are classified as responders or non-responders to treatment with vitamin D metabolites and analogues. Additionally, recent studies have demonstrated the association between mineral metabolism disorders and worse outcomes, suggesting that a better control of theses parameters may improve mortality in CKD patients.[3-5]

Experimental and clinical studies suggest that intravenous paricalcitol, a selective Vitamin D receptor activator, may suppress the synthesis of parathyroid hormone (PTH) at a transcription level;[6,7] this effect is achieved with less impact on the serum Ca and P levels than the effect of the non-selective vitamin D metabolites used to date,[8-10] making it a useful alternative in the treatment of SHPT.

The overall purpose of the study was to assess the effectiveness and safety of intravenous paricalcitol administered over 6 months as per conventional clinical management, with close follow-up of the response to treatment and monitoring of biologic parameters, in patients with SHPT undergoing dialysis who were either naïve to treatment with vitamin D metabolites or who have failed to respond to current therapies.

Methods

Study design

A prospective, multicenter, open-label, non-comparative, phase 4 clinical trial was performed, comparing the clinical and laboratory status of patients before and after 6 months of treatment with intravenous paricalcitol between January 2008 and September 2009.

Location

The study took place in Uruguay and included 5 dialysis centers.

Participants

The initial plan was to recruit 30 patients undergoing chronic hemodialysis (HD) with SHPT diagnosis who were naïve to treatment with vitamin D metabolites or who had failed to respond to the current therapy. Informed consent was obtained prior to participation and was documented in the patient's history according to local regulations.

Inclusion criteria

18 years of age or older, with SHPT defined as serum intact parathyroid hormone (iPTH) levels > 300 pg/mL, in a chronic hemodialysis program; naïve to vitamin D metabolite therapy or patients in which the vitamin D3 treatment has failed, defined by PTH serum levels > 300 pg/mL, high serum Ca levels (> 11 mg/dL) or high serum P levels (≥ 6.5 mg/dL) 3 months prior to recruitment; or poor patient compliance defined as interruption of treatment because of side effects, bad taste, many pills, etc with oral products.

Patients with severe hyperparathyroidism (iPTH levels > 1500 pg/mL); those with known hypersensitivity and/or toxicity to vitamin D metabolites and/or other product ingredients; those who participated in a clinical study within the previous month or were currently enrolled in another clinical trial; those not tolerating or taking Ca- or aluminum-containing or non-containing P binders; those who were pregnant or lactating; those with severe liver failure; and those with confirmed malignancy were excluded from the study.

Efficacy and safety variables

The efficacy of treatment was evaluated by the measurement of serum levels of iPTH (pg/mL) for each patient, recorded at inclusion (baseline) and during follow-up visits. Treatment efficacy was defined as the proportion of patients with at least a 30% reduction in iPTH levels. Safety variables included Ca and P serum levels Ca x P product, serum glutamic oxaloacetic transaminase (SGOT) levels, serum glutamic pyruvate transaminase (SGPT) levels, and complete blood count (CBC).

Other measures included blood urea and serum creatinine to evaluate the dialysis treatment and plasma albumin levels. Hypercalcemia was defined as a serum Ca level ≥ 11.5 mg/dL, hyperphosphatemia was defined as a serum P level > 7.0 mg/dL, and elevated Ca x P product was defined as > 70 mg^2/dL^2.

In all cases, Ca values were corrected based on serum albumin levels. The use of phosphate binders was also recorded and physicians were asked to record the name of the active ingredients, dosages, and the start date of treatment. Basic demographic characteristics and clinical data (concomitant medications, onset of CKD, number and type of prior treatments for SHPT, time on dialysis program, body mass index, heart rate, and blood pressure) were also recorded.

Physicians monitored each subject for clinical and laboratory evidence of adverse events (AEs) on a routine basis throughout the study and recorded any event in detail, including date of onset, description, severity, time course, duration and outcome, relationship to study drug, alternative etiology for events considered not related to study drug, final diagnosis (if known), and any action taken.

A serious AE was defined as any untoward medical occurrence that, at any dose, resulted in the death of the patient, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity.

Follow-up and data collection

Patients were followed for a minimum of 6 months from enrollment. The follow-up period and measurements of studied variables can be summarized in 3 consecutive phases as follows:

During Phase 0 (pre-enrollment and enrollment period), baseline measurements were performed at the beginning of the hemodialysis week (serum levels of iPTH, Ca, P, Ca x P product, albumin, SGOT, SGPT, blood urea, serum creatinine, and CBC). During Phase I (the first 3 months, including the dose titration period), paricalcitol doses were titrated. The titration period was defined as the time to achieve the target iPTH range (150-300 pg/mL) or for a reduction of 30% from initial iPTH levels; thus, the duration of the titration period could be different for individual patients. During this phase, iPTH, Ca, P, and Ca x P product measurements were performed as follows: during the dose titration period, Ca, P, and Ca x P product were measured weekly and iPTH levels were measured every other week; after the dose titration period, Ca, P, and Ca x P product were measured every other week and iPTH levels were monitored on a monthly basis. Measurement of CBC, blood urea, serum creatinine, and albumin were performed monthly, as were SGOT and SGPT levels. During Phase II (the last 3 months), levels of Ca, P, and Ca x P product were measured on a monthly basis, whereas albumin levels and iPTH were measured at months 4 and 6. Routine blood tests were conducted monthly.

All blood samples were collected before starting dialysis session, at the beginning of each week, (during the first dialysis session) and were analyzed in the ensuing 24 hours. A qualified central laboratory performed all laboratory tests. Phosphomolybdate solution in the Alcyon 300i system (Abbott Laboratories, North Chicago, Illinois, USA) was used to determine serum P levels. Serum Ca levels were measured with the Arsenazo III technique using the Alcyon 300i instrument. Measurement of iPTH levels was determined by means of enzyme immunoanalysis using the Immulite 2000 system (Siemens Healthcare, Malvern, Pennsylvania, USA).

The protocol allowed for the prescription of Ca- or aluminum-containing or non-containing phosphate binders throughout the study as needed, with quantification of the use of phosphate binders. Treatment discontinuation was defined as follows: the patient voluntarily decided to leave the study; the occurrence of a serious or non-serious AE that made the suspension of treatment advisable; the patient required treatment that was incompatible with paricalcitol injection (e.g., phosphate compounds, compounds related to Vitamin D, or warfarin); the patient required another treatment that could interfere with the ability to continue in the study; or any other situation that in the physician's opinion made it advisable to withdraw the patient from the study (e.g., the patient's inability to follow medical instructions). For data collection, case report forms (CRFs) were filled out by the physician, and all collected data were entered in an electronic database for statistical analyses.

Data quality assurance

The medical staff of the participating centers provided direct access to original data (including subject history and original pathology reports) to study supervisors to allow data verification and-whenever necessary-CRF corrections. At each visit, supervisors checked the source documents and made sure that investigators were conducting the study according to the protocol and complying with all relevant provisions.

Intervention

Intravenous Paricalcitol was administered as per the Uruguayan prescribing information, following the study protocol. The initial dose for all patients ranged between 0.04 and 0.1 µg/kg and was adjusted according to the individual iPTH level at baseline as follows: 0.04 µg/kg if iPTH levels fell between 300 and 500 pg/mL; 0.07 µg/kg if iPTH levels were between 500 and 800 pg/mL; and 0.1 µg/kg if iPTH levels were > 800 pg/mL. Paricalcitol doses were administered as a intravenous bolus during the HD session, no more frequently than every other day.

If a satisfactory response was not observed, the dose was increased by 2-4 µg at 2- to 4-week intervals, based on the attending physician's judgment. During the dose titration period, levels of Ca, P, and iPTH were measured as described previously. If patient presented with hypercalcemia (serum Ca levels ³11.5 mg/dL), persistent hyperphosphatemia (serum P levels > 7.0 mg/dL), or persistent Ca x P product > 70 mg^2/dL^2, the dose was reduced (or interrupted if necessary) until parameters returned to the normal range. Paricalcitol injection was then to be resumed at lower doses.

If the dose needed to be lowered, it was reduced by 2-4 µg (or 25% of previous dose) at 2- to 4-week intervals, as judged by the attending physician. If a satisfactory iPTH response was not observed and Ca, P, and Ca x P product were not elevated, the dose was again increased by 2-4 µg at 2- to 4-week intervals. If iPTH levels dropped to < 150 pg/mL at any time, the drug was interrupted temporarily or the dose was down-titrated until control of iPTH levels was achieved.

Then, if subsequent measurements of iPTH levels returned to the target range (150-300 pg/mL), the attending physician prescribed the last dose administered; if iPTH levels were maintained < 150 pg/mL, treatment was suspended, and so on. Once the titration dose was reached, it was maintained until the end of the follow-up period.

The paricalcitol injection used in this study was supplied by Abbott Laboratories Uruguay S.A through the pharmacy of each center, regardless of the patient's enrollment in the study. In keeping with the Ministry of Health's recommendations for the conduct of clinical trials, each package containing five 1-mL vials (5 µg/mL each) had a label that read "Drug for Clinical Study- URUG-06-01", the sample's correlative number, regulatory data, and the caption "Only for use in clinical study."

Clinical outcomes of interest

The primary study endpoint was the proportion of patients with at least a 30% reduction in iPTH levels at the end of the follow-up period (the final visit) in comparison to baseline iPTH levels. Secondary study endpoints were to evaluate the safety of paricalcitol injection based on the analysis of major adverse clinical events and/or episodes of hypercalcemia, hyperphosphatemia, and elevations of Ca x P product; and to assess the response time required to achieve a reduction of iPTH levels to the target clinical range (iPTH range, 150-300 pg/mL), consistent with the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines.[11]

Statistical analysis

Continuous variables were calculated as mean/median and standard deviation (SD)/interquartile range, respectively, and were compared using the *t* test or the Mann-Whitney U test. Categorical data were summarized as percentages and were compared using a chi-square or Fisher exact test, depending on the expected values.

Variations of iPTH serum levels for each subject were obtained based on the difference between the value at the end of follow-up period (last visit) and the baseline iPTH level (the baseline value was the reference value). The individual percentage decrease was also calculated in each post-baseline measurement. The mean decreasing percentage of iPTH was reported using 95% confidence intervals (95% CIs). The comparison between iPTH levels at baseline and after treatment was tested using the Wilcoxon non-parametric test for paired samples. A 2-sided $p < 0.05$ was statistically significant.

Determination of sample size

The sample size calculation was based on the primary endpoint, the percentage of patients with at least a 30% reduction in iPTH levels at the end of the follow-up period (*vs*. baseline iPTH levels), assuming a prior estimate of $p = 0.5$ (no prior evidence or unknown), 95% CI for the estimation, and 0.2 as the error estimate or imprecision. A sample size of 24 patients was necessary under these parameters.

Ethics

The protocol of this trial was approved by the Ethics Committee of the School of Medicine of the Universidad de la República (UDELAR). The study materials, all protocol versions, CRFs, and adverse reactions report forms were submitted to and approved by the committee prior to any procedure.

The study was carried out in accordance with the ethical requirements of the Declaration of Helsinki, Scottish review (Edinburgh, October 2000), with the amendments made at the World Medical Association (WMA's) General Meeting, Tokyo 2004, applicable to research involving humans, and in accordance with the Uruguayan Minister of Health's Decree 189/998, Good Clinical Practice of Clinical Pharmacology Investigation.

The decision and initiation of treatment were, at all times, based on the clinical judgment of the researcher. All patients were informed regarding all aspects of the study and their signed consent to participate was required prior to any study-related screening procedures. Investigators were provided with a standard informed consent form that was given to patients prior to their inclusion in to the study, including information on the objectives of the study and its expected benefits and risks, as well as a statement regarding the voluntary nature of participation.

The investigator explained the nature of the study clearly and answered all the questions posed by potential study participants. Patients were informed that they could refuse to participate and would be free to withdraw from the study at any time, without any repercussions. One copy of the signed and dated consent form was given to the patient and the other was kept by the investigator.

Results

In an initial pre-inclusion phase, 26 of the 43 eligible patients met the inclusion criteria and began study treatment. During the follow-up period, 7 patients withdrew from the study (4 because of changes in the dialysis technique or transplantation, 1 patient died, and 2 patients withdrew their consent to continue in the study). The mean duration of treatment for these 7 patients was 2 months; the average dose of paricalcitol administered was 4.6 µg, given no more frequently than every other day. A total of 19 patients completed 6 months of treatment with paricalcitol.

Baseline characteristics of patients

Baseline demographic, clinical and laboratory data of the 19 patients who completed 6 months of treatment with paricalcitol are provided in Tables 1 and 2. Mean initial doses of paricalcitol was 4.21 ± 1.3 ug at the end of the study the paricalcitol doses was 3.1 ± 2.8 ug. An average dose reduction was noted in the second half of the follow-up period.

Efficacy evaluation

An efficacy analysis was performed using data from the 19 patients who completed 6 months of treatment. Seventeen patients (89.5%) achieved a decrease of iPTH levels > 30%. At the end of the follow-up period, all patients showed a significant decrease in baseline iPTH levels ($p < 0.002$), with a mean reduction of 371.8 pg/mL (95% CI, 273.3-470.2). Baseline iPTH levels ranged from 325-1370 pg/mL, with a mean iPTH level of 684 pg/mL (SD, ± 298 pg/mL). Final iPTH levels ranged from 74-928 pg/mL, with a mean value of 312 pg/mL (SD, ± 211 pg/mL). The mean variation in iPTH levels during the observational period is summarized in Figure 1, and individual iPTH variations are shown in Figure 2.

The percentages of iPTH reduction from baseline to the final visit varied from 4%-81%. Therapeutic success (iPTH levels between 150 and 300 pg/mL) at the end of the study period was achieved in 12 patients (63%). The median time to therapeutic success was 2 months (interquartile range, 1-2 months); 7 patients reached the target within the first month of therapy. A higher proportion of patients with a baseline iPTH level < 800 pg/mL achieved therapeutic success compared with those with iPTH levels ≥ 800 pg/mL (87% *vs.* 25%; $p < 0.037$).

Serum Ca levels were evaluated during the 6 months of treatment according to the study protocol. Although there was a significant mean increase in serum Ca levels of 0.6895 mg/dL from month 0 to month 6 (paired *t* test, $p < 0.002$), the mean serum Ca at the end of the study was acceptable. The monthly course of mean serum Ca levels is shown in Table 3 and Figure 3. Mean Ca levels at each observational time (months 1, 2, 3, 4, 5, and 6) were calculated based on data from the last week in the corresponding month (i.e., week 4, month 1; week 4, month 2). None of the subjects showed any clinical symptoms of hypercalcemia.

Table 1 Baseline demographics and patients characteristics

Patients	(n = 19)	
Categorical data	N (%)	
Female sex	10	(52)
Any pulmonary disorder	5	(26)
Chronic obstructive pulmonary disease	3	(16)
Asthma	1	(5)
Tobacco	1	(5)
Any cardiovascular disorder	14	(73)
Hypertension	10	(52)
Ischemic heart disease	4	(21)
Diabetes	2	(10)
Oral calcitriol intake (pre-inclusion)	10	(52)
Quantitative data	Md	(Q1-Q3)
Age at inclusion (years)	61	(52-68)
Weight (kilograms)	70	(60-82)
Time in hemodialysis (months)	53	(32-93)

Md (Q1-Q3), median (first and third quartile, respectively).

Serum levels of P were also evaluated during the 6 months of treatment (Figure 4). There was no significant increase of mean P levels throughout the study. According to the Ca x P product, no differences were observed between the baseline and final visit values (mean Ca x P of 44.44 mg^2/dL^2 at baseline *vs.* 50.1 mg^2/dL^2 at month 6; $p = 0.405$). By the final visit, 16 patients (84%) had obtained Ca x P product levels < 65 mg^2/dL^2.

Safety evaluation

Episodes of hypercalcemia and hyperphosphatemia were summarized for patients who completed the 6 months of treatment as planned. From a total of 283 measurements of Ca serum levels, only 2 episodes of hypercalcemia occurred during the study period (in the same patient), corresponding to rate of 0.7% (according to protocol values defined for hypercalcemia, serum Ca levels > 11.5 mg/dL). Based on the latest K/DOQI guidelines (serum Ca levels > 10.5 mg/dL), the frequency of hypercalcemia was 6.25%.

According to serum P levels, 126 of the 283 measurements obtained (44%) were > 5.5 mg/dL (in accordance with the latest K/DOQI guidelines) and there were 34 episodes (12%) of hyperphosphatemia based on the criteria defined in the protocol (P serum level > 7 mg/dL), which resulted in a transient discontinuation of treatment, as set forth in the protocol. Eleven patients (58%) presented with hyperphosphatemia at least once. The number of episodes of hyperphosphatemia per patient varied from: 4 patients 1 episode, 3 patients 2 episodes, and 4 patients 3 or more episodes.

A safety analysis was performed for all patients who received at least one dose of the study drug; 27 patients were included in the safety analysis. A total of 8 different AEs were observed; 3 AEs (death, cardiac dyspnea, and pneumonia) were classified as serious and 5 AEs (arrhythmia, hyperphosphatemia, hypercalcemia, SGOT and SGPT elevation, and nausea) were classified as not serious. Data regarding AEs are shown in Table 4. Six AEs were considered to be unrelated and 2 AEs were considered to be probably related to the study drug. All of the serious AEs observed were not considered to be related to treatment with the study drug.

The most frequent AE reported was hyperphosphate mia, which was observed in 15 patients; all cases of hyperphosphatemia were asymptomatic and were not considered serious. In 337 measurements of serum P levels of 27 patients in the study, 34 episodes of hyperphosphatemia

Table 2 Baseline laboratory evaluations

	N	Mean	SD	Min	Max
iPTH (pg/mL)	19	684	298	325	1370
Serum calcium (mg/dL)	19	8.8	0.76	7	10.3
Serum phosphorus (mg/dL)	19	5.0	0.92	3.1	6.6
Hemoglobin (g/dL)	19	11.1	0.6	9.0	12.5
Albumin (g/dL)	19	3.92	0.3	3.4	4.6
Blood glucose (mg/dL)	19	114.29	52.5	73	285
SGOT (IU/L)	19	16.2	10.88	8	55
SGPT (IU/L)	19	16.9	21.49	2	102

iPTH, intact parathyroid hormone; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase. SD, standars desviation; Min, minimum; Max, maximum.

Figure 1. Evolution of iPTH levels (pg/mL) during the study period in the 19 patients who completed 6 months of treatment with paricalcitol. Data are expressed as means and 95% CIs.

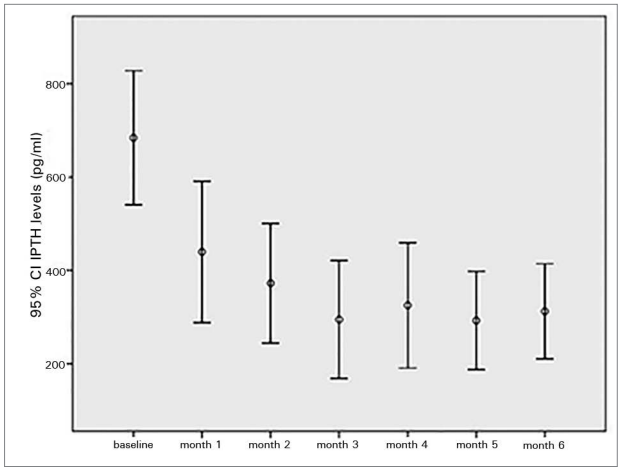


Figure 2. Baseline and month 6 iPTH levels (pg/mL) in the 19 patients who completed 6 months of treatment with paricalcitol.

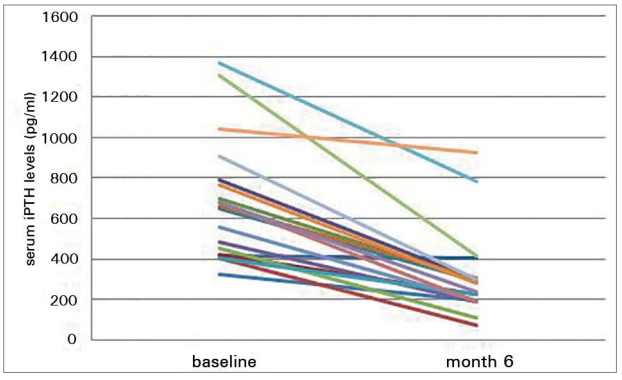


Table 3 Monthly course of mean serum Ca levels

Ca Levels*	Mean	95% CI
Baseline	8.8	8.46-9.20
Month 1	9.4	9.07-9.74
Month 2	9.2	8.97-9.49
Month 3	9.5	8.80-10.30
Month 4	9.5	9.22-9.88
Month 5	9.4	9.16-9.70
Month 6	9.5	9.18-9.86

Ca, calcium; CI, confidence interval. *Mean Ca levels in each observational time (months 1, 2, 3, 4, 5, and 6), were calculated with data from the last week in the corresponding month.

were observed in 15 patients: 6 patients had only one episode, 5 patients had 2 episodes each, and 4 patients had 3 or more episodes; 1 patient presented with 6 episodes. Hypercalcemia was only reported in one patient; this patient experienced 2 episodes. Only one patient experienced mild asymptomatic elevations of SGOT and SGPT levels, with values of

Figure 3. Evolution of serum Ca levels (mg/dL) during the study period in the 19 patients who completed 6 months of treatment with paricalcitol. Data are expressed as means and 95% CIs.

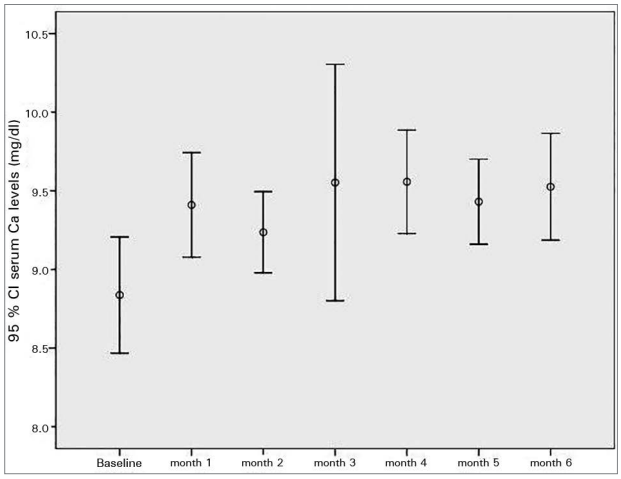
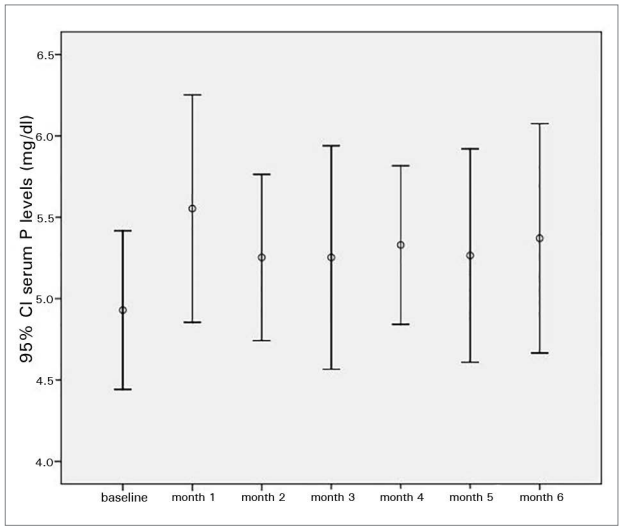


Figure 4. Evolution of serum P levels (mg/dL) during the study period in the 19 patients who completed 6 months of treatment with paricalcitol. Data are expressed as means and 95% CIs.



111 iU/L and 175 iU/L for SGOT and SGPT at month 6, respectively.

Discussion

Disturbances in mineral and bone metabolism are prevalent in patients with CKD and are an important cause of morbidity, decreased quality of life, extraskeletal calcifications, and increased cardiovascular mortality. Data from the Uruguayan Registry of Dialysis,[12] which is a registry of all patients on dialysis since 1980, show a persistent profile of hyperparathyroidism and cardiovascular calcifications, with a low percentage of patients within the suitable range of control of divalent ion metabolism and a low percentage of patients with an adequate treatment of these disorders.

Table 4 Adverse events *

Adverse Event	Related n (%)	Not Related n (%)	Total n (%)
Serious			
Death	0	1 (4)	1 (4)
Cardiac dyspnea or chest pain	0	1 (4)	1 (4)
Pneumonia	0	1 (4)	1 (4)
Not serious			
Arrhythmia	0	1(4)	1 (4)
Hyperphosphatemia	15 (55)	0	15 (55)
Hypercalcemia	1 (4)	0	1 (4)
SGOT and SGPT elevation	0	1 (4)	1 (4)
Nausea	0	1 (4)	1 (4)

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase. *Data from all included patients (n = 27) that received at least one dose of the study drug.

By 2012, of the 2714 patients undergoing HD in Uruguay, only 53.7% had adequate levels of Ca; 40.4% had adequate levels of P; and 38.9% had adequate levels of PTH, according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[13,14]

The combination of high PTH and low 1,25(OH)2D3 is associated with bone loss, cardiovascular disease, immunosuppression, and higher levels of inflammation markers, which help sustain the increases in morbi-mortality. Conversely, treatment of SHPT with vitamin D active compounds has been associated with a reduction of all-cause and cardiovascular mortality.[15-17]

As kidney disease progresses, increasing doses of vitamin D analogues are required to suppress PTH secretion; these increments are limited by increasing values of P and Ca levels. Some observational studies have shown that paricalcitol provides better control of serum iPTH, Ca and P values than calcitriol.[18]

Our study included close monitoring of response and dose adjustment, with consideration of PTH, Ca, and P levels. The results show that paricalcitol treatment is effective, as indicated by a 30% reduction from PTH baseline values in 89.5% of patients. During the 6 months of treatment, 63% of patients achieved therapeutic success. These results are comparable with the results of other studies.[19-21]

Treatment response was achieved in a median duration of 8 weeks, with 7 patients responding within the first month, which is somewhat shorter than the time period required with other active vitamin D derivatives.[22]

Calcium levels increased slightly during the study, but remained within the safety ranges according to the K/DOQI guidelines; most patients maintained normal P levels. Different responses were obtained in patients whose PTH levels at baseline were > 800 pg/mL and < 800 pg/mL. In patients with PTH levels > 800 pg/mL (4 patients), there was only one patient who reached the target level at the final visit (25%). Conversely, 12 of 15 of the remaining patients (75%) had an adequate response by the end of the study. These results are consistent with those reported by the Danish group in their randomized trial, where the best response with paricalcitol was obtained in patients with similar PTH pre-treatment values.[22]

In terms of efficacy and tolerability, our results were also comparable to other observational studies. At the 6-month time point in the Fernström study,[23] 40% of the patients had PTH levels conforming to the K/DOQI target, 7.4% had levels below the target, and 53.7% had levels above the target, with median Ca levels slightly increased and stable serum P levels.

Vitamin D plays a critical role in maintaining mineral homeostasis. Distortions of the balance in terms of Ca, P, PTH, and other elements such as Fibroblast growth factor (FGF- 23) may induce vascular calcification. Moreover, deficiency of vitamin D in its natural and active forms has been considered a potential risk for calcifications, cardiovascular disease, and survival.[24]

Currently, vitamin D receptor activators are considered to play a dual role in vascular calcifications, as supported by recent studies.[25-29] At physiologic levels, vitamin D may have protective effects on the vascular calcification process, mainly through regulation of bone metabolism. Using a mouse model, Mathew *et al.*[30] have shown that while treatment with calcitriol and paricalcitol protected against aortic calcification at dose ranges just sufficient to control SHPT, higher doses could promote calcification. Histomorphometric studies of bone biopsies have prompted these authors to postulate that the skeletal actions of vitamin D receptor activators could explain this "protective" action by reducing osteoblastic gene expression in the aorta and regulating bone formation.

In large populations, some studies have shown the benefits of treatment with paricalcitol compared with calcitriol, not only in the control of Ca and P levels, but also in the effects of CKD and metabolic bone disease.[31,32] Some explanations for this difference may

be drawn from experimental models. In rats with parathyroidectomy and Ca and P dietary restrictions, paricalcitol induced lower increment in Ca and P levels than calcitriol, due to less intestinal Ca and P absorption.

Mechanisms of the role of Ca and P in arterial calcifications were particularly highlighted *in vitro* by Giachelli *et al*.[33-35] Vascular calcification, CKD progression, morbidity, and mortality have been associated with serum P levels within the upper limit of the normal range in experimental and clinical settings.[36,37]

Conversely, PTH increases early in the course of renal disease, even with normal Ca and P levels; it has been shown that FGF-23 can also be increased. Gutierrez and other groups have demonstrated that FGF-23 regulates P metabolism in healthy individuals and patients with CKD, and could be responsible for maintaining low serum levels of P in the early stages of CKD.[38] FGF-23 is a phosphaturic hormone produced by osteocytes, which also downregulates the production of 1-25 vitamin D, and the expression of mRNA Pi and sodium phosphate co-transporters. FGF-23 has also been associated with vascular calcifications, progression of kidney disease, and all-cause and cardiovascular mortality.[39,40]

Analyzing a clinical cohort of 1501 patients, Scialla *et al*.[41] postulated that even though FGF-23 is a marker of increased risk of mortality, it is not associated with and does not induce vascular calcifications in the same way as increases of P. The action of FGR-23-mostly in the cardiovascular system and cardiac hypertrophy, as identified by Faul *et al*.[42] might be explained by a different pathway than the uptake of P or phosphate-induced calcifications. Nakanishi *et al*.[43] proposed FGF-23 levels as a predictor of refractory hyperparathyroidism in patients undergoing dialysis.

Interestingly, at a recent meeting, Kuro-O[44] postulated that extracellular phosphate was toxic to cells at high concentrations when increased in the urine by overload. This may lead to kidney damage (tubular injury and interstitial fibrosis). Extracellular phosphate could exert a cytotoxic effect by forming insoluble nanoparticles with Ca and fetuin A, referred to as calcium protein particles. These particles can induce cellular responses as osteogenic transformation of vascular smooth cells, and have been detected in the blood of animals and patients with CKD. Hence, mineral metabolism, inflammation, vascular calcifications, and aging can be pooled together as determinants of progression of kidney disease.

These observations support the assertion that FGF-23 is a risk marker, but they also highlight the relevance of early control of phosphate in the clinical setting, and the use of therapy to treat chronic kidney disease-mineral bone disorders (CKD-MBD), as identified by de Oliveira *et al*.[45]

This study has some limitations. Our aim was to include in this study 24 subjects but we only included 19 patients. Moreover the follow up period was only 6 months. Finally we erroneously and arbitrarily define hyperphosphatemia as $p > 7$ mg/dl and this value does not match the actual KDIGO guidelines.

In summary, we propose that it is important to study the endocrine axis (PTH, vitamin D, and FGF-23 levels) as glomerular filtrate declines. The results could be beneficial in guiding medical decisions. We also consider the introduction of vitamin D derivatives to be adequate, particularly analogs such as paricalcitol, taking in account its efficacy and tolerance, mainly between PTH levels of 150 and 800 pg/mL.

Conclusion

In conclusion, the results of this study support the use of intravenous paricalcitol as an effective and well tolerated treatment for the control of iPTH levels in hemodialysis patients with SHPT with minimal impact on Ca and P levels.

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