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Original Article

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Treatment with oral paricalcitol in daily clinical practice for patients with chronic kidney disease stage 3–4: a preliminary study

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Abstract

Background. Active vitamin D is an effective treatment for secondary hyperparathyroidism (SHPT) in chronic kidney disease (CKD) patients often complicated by hypercalcaemia and hyperphosphataemia. Treatment with paricalcitol, a selective vitamin D receptor activator, has shown benefits by adequately reducing parathyroid hormone (PTH) levels with minimal changes in serum calcium (Ca) and phosphorus (P). The purpose of this study is to present data on the use of oral paricalcitol in real-life clinical practice in patients with CKD stage 3–4 and SHPT.

Methods. We studied 43 patients, M/F: 25/18, median age: 74 years (47–87), CKD stage 3/4: 16/27, with SHPT, who were prescribed oral paricalcitol at recommended doses for 6 months. Monthly measurements of serum intact PTH (iPTH), Ca, P, alkaline phosphatase (ALP), haemoglobin, albumin (ALB), lipid profile, proteinuria and 24-h urine creatinine clearance were performed 3 months before and 6 months after treatment initiation.

Results. Paricalcitol induced a significant, early and sustained, through the end of follow-up period, decrease in iPTH and ALP levels and an increase in serum ALB. No significant increase in Ca and P levels as well as in Ca × P product was observed during the study period. No significant changes were found in protein excretion, kidney function and the other measured parameters between baseline and last evaluation. Paricalcitol final median dose was 5 μg/week ranging between 3 and 7 μg/week.

Conclusions. In the context of real-life clinical practice, oral paricalcitol for 6 months is an effective, well-tolerated treatment of SHPT in CKD stage 3–4 with minimal effects on calcium and phosphorus metabolism.

Keywords: CKD stage 3 and 4; secondary hyperparathyroidism; oral paricalcitol; parathyroid hormone; vitamin D

Introduction

Secondary hyperparathyroidism (SHPT) develops early in the course of chronic kidney disease (CKD), when glomerular filtration rate (GFR) falls <70 mL/min/1.73 m^2 and progresses as renal function further declines [1]. The pathogenesis of SHPT in patients with CKD is multifactorial. Active and native vitamin D deficiency, hypocalcaemia, phosphorus (P) retention and fibroblast growth factor-23 (FGF-23) accumulation, skeletal resistance to parathyroid hormone (PTH) and vitamin D action, decreased number and down-regulation of several related receptors [vitamin D receptors—VDRs, calcium (Ca)-sensing receptors, FGF-23/Klotho] lead to excessive synthesis and secretion of PTH and, subsequently, to the development of SHPT and renal osteodystrophy. Newly discovered humoral factors such as FGF-23 and proteins involved in FGF-23 signalling such as Klotho appear to play an important role in the pathophysiology of mineral metabolism and SHPT and may represent potential future therapeutic targets [2–4].

In current clinical practice, the treatment of SHPT involves normalizing serum P, by appropriate diet combined with the administration of P-binders that block the intestinal absorption of dietary P and restoration of vitamin D levels by replacement therapy. Calcitriol [1α,25$(OH)_2D_3$] and alphacalcidol [1α $(OH)D_3$] have been extensively used for the prevention and treatment of SHPT in patients with CKD. In clinical trials, both forms of vitamin D have been shown to be effective in lowering PTH levels although their use is relatively frequently complicated by hypercalcaemia, hypercalciuria and hyperphosphataemia with a consequent increased risk of vascular calcification and renal function deterioration. A vitamin D analogue reducing PTH levels with a minimum effect on Ca and P metabolism would be an ideal candidate for more effective and safer control of SHPT [5]. Therefore, selective VDR activators have been developed to inhibit PTH

secretion with less effect on the intestinal absorption of Ca and P. Paricalcitol, 19-nor-1,25$(OH)_2D_2$, is the most commonly used of these analogues. Its tissue selectivity has been attributed to the presence of vitamin D_2 side-chain instead of the D_3 side chain of calcitriol and to the lack of the exocyclic carbon at the 19th position [6, 7].

The majority of studies to date have evaluated the effectiveness and safety of paricalcitol, used in the intravenous formulation, in patients with end-stage renal disease on haemodialysis (HD) with favourable results. However, the intravenous route of administration is convenient only for HD patients and not for CKD stage 3–5 pre-dialysis or peritoneal dialysis patients [8–14]. Oral paricalcitol has been established as effective and safe treatment of SHPT in pre-dialysis patients [15]. However, post-approval studies on the effects of oral paricalcitol in the real-life clinical setting are largely lacking and the relevant clinical experience is limited. Furthermore, the results from large clinical trials are not always easily applicable to everyday clinical conditions. The purpose of this observational prospective single-centre study is to evaluate the use of oral paricalcitol in CKD stage 3 and 4 patients with SHPT in daily clinical practice.

Materials and methods

Patients aged 18 years and older with CKD stage 3 and 4 (estimated MDRD GFR 30–59 mL/min/1.73 m^2 and 15–29 mL/min/1.73 m^2, respectively) and SHPT [iPTH >7.7 pmol/L (70 pg/mL) for CKD stage 3 and >12.1 pmol/L (110 pg/mL) for CKD stage 4] were eligible for the study.

Patients were excluded on evidence of significant comorbidity such as malignancy or if they had received medications that might alter calcium or bone metabolism such as calcitonin, bisphosphonates, glucocorticoids or other vitamin D compounds within 3 months prior to inclusion into the study. The study was performed in accordance with the Declaration of Helsinki and local Ethics Committee decided that approval was not required. All patients gave written informed consent before enrolment.

The primary objective was to evaluate iPTH level changes in CKD stage 3–4 patients with SHPT receiving oral paricalcitol. Secondary objectives were to assess the incidence of abnormalities in serum Ca and P levels and the changes in proteinuria, renal function and commonly assessed haematological/biochemical parameters. Furthermore, the changes in the above-mentioned variables were assessed in the subgroups of patients such as diabetics/non-diabetic, males/females and CKD3/CKD4. Finally, data on adverse events were collected and evaluated.

Table 1. Patients demographic characteristics[a]

Age (median, range, years)	74 (47–87)
Male/Female (*n*)	25/18
Cause of CKD (*n*)	
DN	14
Nephrosclerosis	6
PKD	2
Unknown	21
Diabetics (*n*)	18
CKD stage 3/4 (*n*)	16/27
On ACEi or ARBs (*n*)	18

[a]CKD, chronic kidney disease; PKD, polycystic kidney disease; DN, diabetic nephropathy; ACEi, angiotensin-converting-enzyme inhibitor; ARBs, angiotensin receptor blockers.

Monthly measurements of serum iPTH (immunochemiluminescence intact hormone assay, Modular E170, Roche Diagnostics Corporation, Indianapolis, IN), total corrected Ca, P, alkaline phosphatase (ALP), haematocrit, haemoglobin (HB), total protein, albumin (ALB), total cholesterol (TCHOL), triglycerides (TG), HDL/LDL-cholesterol (HDL/LDL-CHOL) and 24-h urinary protein excretion (24 h-UPROT) were performed 3 months before and 6 months after treatment initiation. At the same time intervals, Ca × P product and clearance creatinine by 24-h urine collection (CrCl) were calculated.

The initial paricalcitol dose was determined according to the baseline iPTH levels and subsequently was adjusted based on the serum PTH, Ca and P levels. Accordingly, the initial paricalcitol dose was 1 μg/day when baseline iPTH ≤56 pmol/L (500 pg/mL) and 2 μg/day when baseline iPTH >56 pmol/L (500 pg/mL). If the reduction in iPTH was <15%, the dose was doubled. If the reduction was between 15 and 60%, it was maintained, and if the reduction was >60%, it was halved. Serum Ca and P levels were closely monitored after initiation of treatment and during dose titration periods. If persistently elevated serum Ca levels >2.6 mmol/L (10.5 mg/dL) or Ca × P product >4.4 $mmol^2/L^2$ (55 mg^2/dL^2) were observed, the paricalcitol dose was reduced or temporarily interrupted. If interrupted, the drug was restarted when serum Ca and Ca × P product were in the target range. In case a patient was taking the lowest daily dose and a dose reduction was required, the dosing frequency was decreased.

Data are reported as mean ± SD unless otherwise stated. The baseline values for all parameters were defined as the mean of data during the pre-treatment trimester. A paired *t*-test was used to assess the mean difference between each treatment month and baseline. Multiple regression analysis was used to assess correlations. P-values <0.05 were considered statistically significant.

Results

Forty-three patients who met the inclusion criteria and had completed 6 months of treatment with oral paricalcitol were included in the analysis. Demographic characteristics of the study population are listed in Table 1.

Pre-treatment (baseline) values of iPTH were consistent with moderate-to-severe SHPT (2.5–4 times the upper normal limits for each CKD stage). iPTH levels at every treatment month were significantly lower compared with baseline values. The greater reduction in the mean

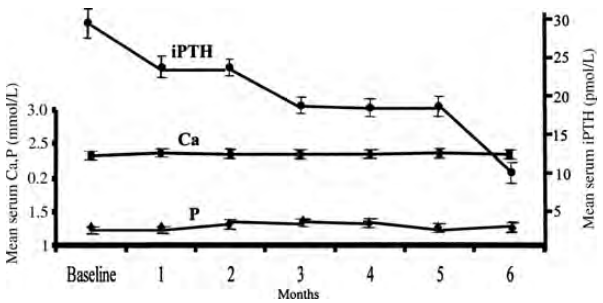

Fig. 1. Serum iPTH, Ca and P levels during the study period. Data presented as mean ± SE.

monthly iPTH levels (20.4%) was noted between baseline and the first treatment month [30.07 ± 14.30 pmol/L (282.6 ± 134.4 pg/mL) versus 23.94 ± 12.14 pmol/L (225.0 ± 114.1 pg/mL), P < 0.001] and the maximum mean decrease [44.9%, from 30.07 ± 14.30 pmol/L (282.6 ± 134.4 pg/mL) to 10.01 ± 8.25 pmol/L (156.4 ± 77.5 pg/mL), P < 0.001] between baseline and the end of the study (Figure 1).

Small non-significant increases in serum Ca levels were observed during treatment with a mean increase, between baseline and last month, of only 0.025 mmol/L (0.1 mg/dL) (Figure 1). During the treatment period, none of the patients reached serum Ca levels of >2.7 mmol/L (10.8 mg/dL). There was a significant decrease in serum ALP from the fourth treatment month (234.3 ± 79.8 versus 257.6 ± 88.0 U/L at baseline, P < 0.001) until the end of the study (220.8 ± 73.9 U/L, P < 0.001) (Figure 2). No significant differences were found in mean serum P levels (Figure 1) and Ca × P product between baseline and all treatment months. Ca × P product >3.6 $mmol^2/L^2$ (45 mg^2/dL^2) was noted in only three patients but none showed levels >4.4 $mmol^2/L^2$ (55 mg^2/dL^2).

Paricalcitol final median dose was 5 μg/week, ranging between 3 and 7 μg/week. The reduction in iPTH levels during the study allowed a lower dose of paricalcitol to be used, from 7.2 ± 2.6 μg/week at baseline to 6.5 ± 3.1 μg/week at Month 3 and 4.9 ± 2.9 μg/week at the end of the study (Month 6).

At the end of the study, a small non-significant decrease in 24 h-UPROT and in CrCl (Table 2), although patients with proteinuria >1.5 gr/24 h were 8/43 (18.6%) at baseline and 11/43 (25.6%) by the end of the study. Paricalcitol treatment did not markedly affect HB, TCHOL, TG or HDL/LDL-CHOL levels. Serum ALB showed a significant increase by the end of the study period (Table 2).

At the end of the study, there were no significant differences in the studied parameters between diabetics and non-diabetics, males and females, angiotensin-converting-enzyme inhibitor (ACEi)/ angiotensin receptor blockers (ARBs) users and ACEi/ARBs free, as well as between CKD stage 3 and 4 patients, with the exception of a marked drop of TCHOL in the group of ACEi/ARB-free patients [from 4.86 ± 0.84 mmol/L (187.9 ± 32.4 mg/dL) to 4.55 ± 0.70 mmol/L (175.9 ± 27.03 mg/dL), P = 0.03]. Paricalcitol dose by the end of the study positively correlated with baseline iPTH levels ($R^2 = 0.999$, P < 0.01).

No major adverse events were recorded during the study. Transient symptoms of gastrointestinal discomfort were reported in two patients that did not necessitate treatment withdrawal.

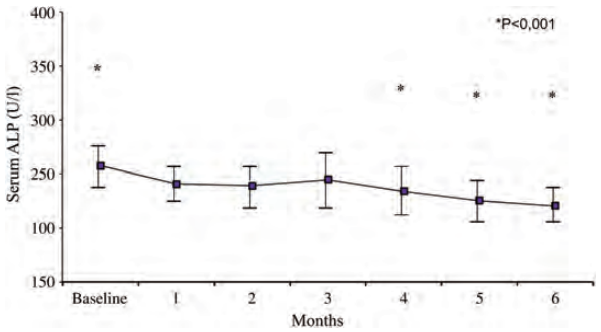

Fig. 2. Serum ALP levels during the study. Data presented as mean ± SE.

Discussion

We present the preliminary results of a prospective study on the use of oral paricalcitol in CKD stage 3 or 4 patients with SHPT under routine clinical practice conditions in a single centre. Our results suggest that this selective VDR activator provides a rapid and sustained reduction of iPTH and ALP without any significant increase in Ca and P levels. Paricalcitol capsules were prescribed in this study on an on-label basis in an everyday setting and we collected data on treatment effectiveness and safety, dose requirements and tolerability, as well as maintenance of the results over a 6-month period in order to obtain experience in the short term use of oral paricalcitol in CKD stage 3–4 patients. Additionally, this study allows us to observe actions of oral paricalcitol in a distinct geographic region (Greece) with >250 sunny days/year.

A progressive loss of kidney function leads to a reduced production of $1,25(OH)_2D_3$ (calcitriol), abnormal mineral homeostasis reflected mainly by an imbalance in both serum Ca and P levels and, eventually, to the development of SHPT and renal osteodystrophy. The importance of these CKD-associated mineral and bone disturbances has been increasingly acknowledged and greatly associated with the progression of renal failure, as well as with increased rates of cardiovascular events and mortality [7,14]. Although administration of active vitamin D, such as calcitriol, decreases PTH levels, it is also associated with elevated Ca × P product. Therefore, selective VDR activators, such as paricalcitol, potentially reducing Ca–P toxicity positively affecting pathogenic mechanisms of vascular calcification, might enhance cardiovascular and renal protection, and thus provide a significant clinical benefit [3].

Prior to our study, there have been only three studies on paricalcitol in CKD stage 3 and 4 patients [15–17]. Coyne *et al.* [15] analysed data from three prospective, randomized, placebo-controlled trials and found that 91% of patients treated with oral paricalcitol reached two consecutive reductions in iPTH levels of ≥30% versus 13% of placebo patients (P < 0.001), while hypercalcaemia and hyperphosphataemia incidence was not significantly different between the two groups. A study by Kovesdy *et al.* [16], comparing paricalcitol and ergocalciferol, found that paricalcitol was more effective at decreasing

Table 2. Changes in secondary study variables between baseline and month 6[a]

	Baseline	Month 6	P
HB (g/L)	118 ± 13	116 ± 12	NS
(g/dL)	11.8 ± 1.3	11.6 ± 1.2	
ALB (g/L)	36.6 ± 4.5	38 ± 3.9	<0.001
(g/dL)	3.66 ± 0.45	3.8 ± 0.39	
TCHOL (mmol/L)	4.77 ± 0.89	4.63 ± 0.95	NS
(mg/dL)	184.5 ± 34.7	178.9 ± 36.8	
TG (mmol/L)	1.58 ± 0.72	1.52 ± 0.81	NS
(mg/dL)	140 ± 64.1	134.5 ± 71.7	
LDL-CHOL (mmol/L)	2.68 ± 0.71	2.67 ± 0.7	NS
(mg/dL)	103.8 ± 27.5	102.9 ± 27.2	
HDL-CHOL (mmol/L)	1.17 ± 0.34	1.24 ± 0.36	NS
(mg/dL)	45.3 ± 13	48 ± 14.1	
24 h-UPROT (g/24 h)	1.20 ± 1.86	1.04 ± 1.38	NS
CrCl (mL/min)	27.3 ± 8.9	25.8 ± 9.8	NS

[a]HB, haemoglobin; ALB, albumin; TCHOL, total cholesterol; TG, triglycerides; HDL/LDL-CHOL, LDL/HDL cholesterol; 24 h-UPROT, 24-h urinary protein excretion; CrCl, creatinine clearance.

iPTH levels with no difference in the episodes of hypercalcaemia and hyperphosphataemia. Sánchez *et al*. [17], in a retrospective observational study performed under routine clinical practice conditions similar to ours, found that the main objective of the study (two consecutive iPTH reductions of 30% from baseline) were achieved in 54% of the treated patients. Mean Ca and P variations during this study were also not significant.

A significant decrease of 44.9% in mean iPTH from baseline to the end of the study was noticed in our group. Coyne *et al*. [15] found a similar iPTH decrease in the paricalcitol groups they analysed with a maximum mean decrease of 45.2%. In our study, the greater iPTH reduction during treatment was found between baseline and first month. This is in agreement with previous studies in CKD stage 3 and 4, as well as in dialysis, patients showing that the major decrease in iPTH levels occurred in the first 1 to 2 months of treatment with less effect thereafter [15–17].

Although vitamin-D metabolites have shown proven efficacy at achieving suppression of elevated iPTH levels in CKD patients, hypercalcaemia and hyperphosphataemia frequently complicated their use. A high Ca × P product predisposes to extraosseous calcifications, including arteries and cardiac valves, associated with high morbidity and mortality [18]. Bianchi *et al*. [19], using a constant calcitriol dosage of 0.25 and 500 mg/day of calcium carbonate noted an increment of serum Ca levels from a baseline value of 8.5 ± 0.3 to 9.9 ± 0.2 mg/dL. Ritz *et al*. [20] reported no change in serum Ca levels with a daily calcitriol dose of 0.125 μg, but iPTH levels also remained unchanged. Hamdy *et al*. [21], in a placebo-controlled trial, showed that alfacalcidol significantly increased the mean serum Ca levels in patients with mild-to-moderate CKD after 4 weeks of treatment and this change persisted until the end of the study (24 months).

It is well established that selective VDRs activation with paricalcitol decreases the intestinal absorption of Ca and P and diminishes the risk of hypercalcaemia and hyperphosphataemia [3]. In Coyne's analysis, the incidence of hypercalcaemia, hyperphosphataemia and elevated Ca × P product was not significantly different between patients treated with paricalcitol and placebo [15]. Similarly, in Sánchez's study [17], among 92 patients who completed a 6-month treatment period, only 5 (5.4%) showed serum Ca levels >10.2 mg/dL and 2 (2.1%) >10.5 mg/dL. Kovesdy *et al*. [16] found non-significant changes in serum Ca and P levels over a 16-week period in both paricalcitol and ergocalciferol subgroups. Hypercalcaemia was only recorded on one occasion for each group, with hyperphosphataemia recorded in 9.7% of patients using paricalcitol and 10.9% of patients on ergocalciferol [16]. Our findings are similar to those of the above-mentioned studies with no significant increases in Ca and P or in Ca × P product during our follow-up period. None of our patients reached Ca levels >2.7 mmol/L (10.8 mg/dL) and in only three cases, the Ca × P product was found to be >3.6 $mmol^2/L^2$ (45 mg^2/dL^2). Minimizing these adverse effects leads to an uninterrupted SHPT treatment with a gradual fall in iPTH levels and, subsequently, may prevent recurrent parathyroid gland growth [5].

CKD progression is another potentially harmful side effect of active vitamin D treatment [22]. Trials using calcitriol at a dose of 0.5–1.0 μg/day reported an increase in serum creatinine levels compared with placebo groups, both in patients with normal baseline renal function and in those with pre-existing renal impairment [23–26]. On the contrary, no such increments in serum creatinine or reductions in creatinine clearance were found in those using lower calcitriol doses in the order of 0.125 or 0.25 μg/day [19,27,28]. According to our data, no difference in creatinine clearance was found between the start and the end of the follow-up period. This finding is consistent with recent studies showing no changes in renal function during oral paricalcitol treatment [15–17]. However, trials with longer follow-up periods are needed in order to conclusively determine the effect of oral paricalcitol on renal function.

Potential influence of various other factors (diabetes status, sex, ACEi or ARBs use, CKD stage) on biochemical parameters during oral paricalcitol treatment was not detected in our group of patients, with the exception of a marked drop of TCHOL in the group of ACEi/ARBs free patients. In the Spanish study by Sánchez *et al*., no significant difference between diabetics and non-diabetics regarding iPTH decrease was found as well. On the contrary, a significant difference was found in this study between patients with CKD stage 3 and those with stage 4, as the primary endpoint of efficacy was achieved in a larger proportion of patients with CKD stage 4 [17]. TCHOL and HDL/LDL cholesterol levels indicate a relatively controlled lipid profile in most of our patients. No significant difference in lipid profile indices was found between baseline and the end of the study, in agreement with the results of Sanchez's study [17]. On the contrary, ALB levels showed a significant increase under oral paricalcitol treatment in our study. A better control of SHPT with oral paricalcitol may have led to an improved nutritional status. In agreement with this observation, a Japanese study by Shidare *et al*. showed that PTH (7–84), but not PTH (1–84), significantly correlated with ALB levels [29].

Paricalcitol decreases proteinuria in patients with proteinuric renal disease [30–32]. In general, vitamin D regulates systems that play an essential role in the pathophysiology of proteinuria. Therefore, paricalcitol inhibits renal inflammation by promoting VDR-mediated sequestration of NF-κB signalling, leading to a reduced renal infiltration with macrophages and a decreased expression of pro-inflammatory cytokines [33]. In addition, paricalcitol reduces podocyte injury by inhibiting Wnt expression and blocking β-catenin-mediated gene transcription [34]. A recent meta-analysis [35] confirmed that paricalcitol lowers proteinuria in patients CKD stage 2–5. Our results showed a non-significant drop of 24 h-UPROT in our patients during a 6-month follow-up period. However, the small number of patients with relatively significant proteinuria (24-h proteinuria >1.5 g) included in our study makes difficult the interpretation of this finding.

In conclusion, the present preliminary prospective study indicates that treatment with oral paricalcitol under the routine, real-life clinical practice conditions is effective at reducing iPTH levels among adult CKD stage 3–4 patients with SHPT. Moreover, calcium and phosphorus levels consistently remained within safety limits. This uncomplicated iPTH decrease potentially protects from the major consequences of chronically elevated iPTH levels regarding bone loss, fractures and cardiovascular disease. Kidney function remained stable and a non-significant decrease in proteinuria was detected during this short follow-up period. Our results are comparable with those of published randomized controlled trials. However, observational studies with a longer follow-up period and larger sample are definitely needed

in order to secure the effectiveness and safety of oral paricalcitol treatment for CKD 3–4 patients under normal clinical practice conditions.

Conflict of interest statement. None declared.

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