

Clinical Research

Role of Vitamin D Receptor Selective Activator Paricalcitol in Nephroprotective Strategy in Chronic Kidney Disease

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Abstract

In this study, we evaluated the comparative effects of calcitriol and paricalcitol in decreasing proteinuria and preventing secondary hyperparathyroidism in patients with chronic kidney disease (CKD), at stages 3-4. Evaluation was done using 50 patients with stages 3-4 of CKD, resulting from connective tissue diseases. 35 patients have systemic lupus erythematosus and 15 patients have various forms of systemic vasculitis. All patients were divided into two groups. Group 1 consisted of 28 patients treated with calcitriol at a dose of 0.25 micrograms per day, while Group 2 consisted of 22 patients, received paricalcitol in a daily dose 1 microgram. All patients on admission and at the end of the study period underwent a Doppler ultrasound of the common carotid arteries. Application of paricalcitol in predialysis stages of CKD with the secondary hyperparathyroidism (SHPT) was accompanied by normalization of intact parathyroid hormone (iPTH) levels, and a significant decrease in the daily proteinuria levels as well as hypertension. *IJBM* 2011; 1(4):199-203. © 2011 International Medical Research and Development Corporation. All rights reserved.

Key words: *chronic kidney disease, secondary hyperparathyroidism, parathyroid hormone, proteinuria, paricalcitol.*

Introduction

Nephroprotective strategy on the predialysis stages of CKD is aimed at the maximal reduction of proteinuria (microalbuminuria) level and the simultaneous therapy of arterial hypertension (AH), as they are the most serious factors of the progression of glomerulosclerosis and tubulointerstitial fibrosis, leading to the development of renal failure. The early and systematic use of calcitriol in combination with renin-angiotensin system (RAS) blockers, as well as lipid-lowering drugs and erythropoietin therapy plays an important role for nephroprotection. Therefore, the primary goal of treatment is to reduce the mortality rate in CKD patients with terminal uremia, and complications of renal replacement therapy, as well as the extrarenal manifestations of CKD, primarily from cardiovascular disease.

Impairment of the vitamin D homeostasis in CKD patients is detected at an early stage of renal failure. The majority of patients with CKD stage 3 could be noted a relative deficiency of the active metabolite of vitamin D₃ – calcitriol (1,25-(OH)₂D₃) in the blood. In the further progression of renal function impairment, falling the level of glomerular filtration rate (GFR) below 50 ml/min/1.73 m² in children and 30 ml/min/1.73 m² in adults could be an indicator of developing total calcitriol deficiency. The progression of CKD is accompanied by a decrease in the number of Vitamin D receptors (VDR) and calcium-sensitive receptors (CaR) in the parathyroid glands (PTG). Simultaneously, there is also a decrease in the PTG sensitivity to the calcitriol and Ca²⁺. Vitamin D levels in the blood may be low in CKD patients with proteinuria due to loss of 25(OH)D₃ with the urine [1, 2].

Calcitriol suppresses PTG, causing a decrease in the transcription and synthesis of the parathyroid hormone (PTH), while it increases the sensitivity of the CaR on the PTG cells, thus blocking the mechanisms of secondary hyperparathyroidism (SHPT) development. Experimental studies have shown that calcitriol deficiency may initiate SHPT development even in the absence of hypocalcaemia [1, 2].

Evidence is now available that the beneficial effects of calcitriol on kidney function are due to the increase of

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expression of transmembrane form of renoprotective Klotho's protein [3] in proximal tubules. However, as it has been noted in clinical studies, administering of calcitriol accompanied with a number of side effects, some of which are listed below:

- due to the increase in the absorption of calcitriol in the gastrointestinal tract there is a consequent increase in the calcium and phosphorus levels in the blood serum, which in turn may increase the calcification of the soft tissues, including the heart and blood vessels;
- pharmacological doses of calcitriol can cause damage of blood vessels endothelium, causing inflammation;
- excessive suppression of PTH may transform SHPT to adynamic skeletal disease.

Now, paricalcitol is the only drug in the group of vitamin D preparations, which satisfy to the objectives of nephroprotection, as well as prevention and treatment of SHPT. Paricalcitol is a metabolite of vitamin D₂ (1,25(OH)₂D₂, whose structure contains a modified side chain (D₂) and ring A (19-nor). Paricalcitol selectively induces the expression of VDR (S-VDRA) gene in PTG by

suppressing the secretion of PTH, but does not activate the VDR in the intestine and has almost no effect on bone resorption, and therefore, is less likely than calcitriol to cause hypercalcemia [1].

Objective

To study the comparative effects of calcitriol and paricalcitol on proteinuria level decreasing and prevention of SHPT in stage 3-4 of CKD caused by systemic connective tissue diseases.

Material and Methods

The study included 50 patients with CKD, at stages 3-4, caused by systemic connective tissue diseases. 35 patients have systemic lupus erythematosus and 15 patients have various forms of systemic vasculitis. To realize of the study objectives all patients were divided into two groups (Table 1).

Table 1

Distribution of patients based on the CKD stage

Groups of therapy	Stage 3 of CKD (GFR: 30-59 ml/min/1.73 m ²)	Stage 4 of CKD (GFR: 15-29 ml/min/1.73 m ²)
1 st group, calcitriol, (n=28)	8	20
2 nd group, paricalcitol, (n=22)	9	13
Total	17	33

The first group included 28 patients treated with calcitriol (Rocartrol[®], Hoffmann-La Roche) at a dose of 0.25 micrograms per day for six months.

The second group consisted of 22 patients treated with paricalcitol (Zemplar[®], Abbott Laboratories) in a daily dose 1 microgram for six months.

Calcitriol and paricalcitol for nephroprotection were to be administered when the level of the intact parathyroid hormone (iPTH) in the blood was not less than 65 pg/ml, and taking into account the indicators of calcium and phosphorus metabolism [8]. All patients received Monopril, an angiotensin-converting enzyme inhibitor, erythropoietin drugs, iron, and statins.

Statistical analysis of the study results performed using the SPSS 10 software package for Windows. Frequencies of individual values, mean, standard deviation of the mean, student's *t*-test, confidence level, and the level of significance *p* were calculated.

Results

Before treatment, proteinuria levels in the first and second groups were 1.2±0.6 g/day and 1.3±0.4 g/day, respectively, and the levels of iPTH were 75±17.4 pg/ml

and 80±16.6 pg/ml, respectively (Table 2). The combined lesion with atherosclerosis/calcification (A/C) of the common carotid artery was revealed in 14.3% of patients in Group 1 and in 22.7% in Group 2.

Calcitriol and paricalcitol were tolerated quite well. After the three months of therapy with both drugs in patients initially having elevated level of iPTH in the blood, normalization of blood iPTH level was achieved.

In patients treated with paricalcitol, a significant reduction in proteinuria (*p* < 0.05) was noted. Combined use of monopril and paricalcitol, unlike calcitriol, lead to more significant decrease of blood pressure (ΔBP) and reduction of the left ventricular mass index (ΔLVMI) (Table 3).

During the observation period, in 22.7% of patients of Group 2 with diagnosed A/C there were no episodes of hypercalcaemia and progression of the A/C. In 35.7% of patients of Group 1, episodes of hypocalcaemia were noted, and 14.3% of patients demonstrated A/C progression.

Thus, using paricalcitol in predialysis stages of CKD with SHPT resulting from connective tissue diseases accompanied with normalization of the iPTH levels, and a significant decrease of proteinuria level and blood pressure.

Table 2

Influence of therapy with calcitriol or paricalcitol on concentration of iPTH in the blood and daily proteinuria in patients with CKD (stages 3-4) resulting from connective tissue diseases

Parameter	1 st group, n=28		2 nd group, n=22	
	Before treatment	After treatment	Before treatment	After treatment
iPTH (pg/ml)	75±17.5	66±12.2	80±16.6	65±14.4
Proteinuria (g/day)	1.2±0.6	0.8±0.32	1.3±0.4	0.3±0.21*

Note: the differences were statistically significant when compared with the indicators of the 1st group: *-p<0.05

Table 3

Dynamics of BP and LVMI in patients with CKD (stages 3-4) on combined therapy with monopril and calcitriol or paricalcitol

Groups of therapy	ΔBP (mm Hg)		ΔLVMI	
	systolic	diastolic	men	women
1 st group, monopril+calcitriol (n=28)	-20.1±2.89	-11.9±1.82	-6.6±3.14	-5.9±3.58
2 nd group, monopril+paricalcitol (n=22)	-23.3±3.21	-12.8±2.03	-20.6±4.25*	-21.3±3.06*

Note: The differences were statistically significant when compared with the indicators of the 1st group: *-p<0.05

Discussion

The antiproteinuric effect of paricalcitol confirmed in 3 double-blind, randomized, placebo-controlled trials, including 220 patients with CKD at stages 3-4 and SHPT. By the end of 24 weeks of observation, decrease of proteinuria level observed in 51% of patients treated with paricalcitol and only in 25% of the patients receiving placebo (p=0.004). The antiproteinuric effect of paricalcitol did not depend on the age, sex, race of patients or concomitant diseases (diabetes, hypertension) [2]. Decrease of PTH up to 30% was noted in 91% of patients treated with paricalcitol, compared with 13% of patients receiving the placebo (p<0.001). Also, decrease of the iPTH level to <110 pg/ml observed in 75% of patients receiving paricalcitol, and in 12% of patients receiving the placebo [1].

It was established that paricalcitol corrects intraglomerular hypertension by inhibiting the RAS. It also reduces the synthesis of renin, ET-1 receptors and inhibits mesangial cell proliferation, hypertrophy of podocytes, and increases the expression of megalin and nephrin. In combination with Losartan, paricalcitol the most expressed nephroprotective effect could be achieved. A follow-up morphological study of the kidneys after six months of treatment revealed a slowdown of glomerulosclerosis and tubulointerstitial fibrosis development. The high efficacy of such combination could be explained by a more expressed decrease of prorenin level in blood with the suppression of the expression of its cellular receptors, as well as immunomodulatory effect of paricalcitol on T-lymphocytes [1]. In experimental study paricalcitol increased expression of the renoprotective Klotho's protein in kidneys [3]. Generally, use of paricalcitol in CKD could result to nephroprotection. However, to confirm this hypothesis, further clinical investigations are necessary.

According to the literature, the cardioprotective effect of paricalcitol expressed in regression of left

ventricular hypertrophy (LVH) and congestive heart failure (CHF) with a decrease of mortality in both patients with predialysis stages of CKD and patients on regular hemodialysis (HD). Three-year retrospective analysis of outcomes of treatment with paricalcitol in 67,000 patients on HD showed their survival rate was 16% higher when compared to patients treated with calcitriol [4, 5]. This increase of survival rate did not correlate with the duration of HD sessions and level of calcium, phosphate and lipids in blood but mainly was associated with more rapid suppression by paricalcitol of PTH secretion, molecular mechanisms of artery calcification, RAS inhibition, decreased expression of the proinflammatory cytokines in myocardium and vascular endothelium (Table 4) [8].

The high efficacy of combination of perindopril with indapamide in multicenter four-year ADVANCE study was demonstrated in more than 11,000 patients with type 2 diabetes mellitus who were assigned to more aggressive control of hypertension and glycemia [6]. In this case, there was a significant decrease in the total and cardiovascular mortality, and complications caused by micro- and macroangiopathy. The incidence of microalbuminuria (proteinuria) and the progression of CKD decreased by more than 20%. To enhance the antiproteinuric effect of the ACE inhibitors, the authors recommend a combination of ACE inhibitors with indapamide, statins, epoetin and paricalcitol.

In a placebo-controlled study [4], which include of 78 dialysis patients, decrease of PTH level were achieved in 68% of patients treated with paricalcitol, compared to 8% of patients in the placebo group (p<0.001). At the same time, in patients with SHPT treated with paricalcitol, the iPTH level decreased from 795 pg/ml to 406 pg/ml (p<0.001), whereas no significant decrease of iPTH level in placebo group was observed (680 pg/ml vs 592 pg/ml).

In a long-term prospective open 16-month study estimated treatment efficacy with paricalcitol in 37 patients with SHPT on regular HD and resistant to calcitriol [7].

Table 4

Influence of paricalcitol on the expression of genes associated with arteries calcification and cytokine-induced inflammation in myocardium and vascular endothelium

Factors associated with calcification	Effect of paricalcitol	Cardiovascular effects
Plasminogen activator inhibitor-1 (PAI-1)	Decreasing of mRNA expression in coronary artery smooth muscle cells	Reducing the incidence of cardiovascular diseases
Thrombospondin-1	Decreasing of mRNA expression	The suppression of thrombogenicity,
Thrombomodulin	Decreasing of protein expression	Intensification of fibrinolysis,
Osteoblast-specific transcription factor – core-binding factor $\alpha 1$	No influence on the expression of mRNA in animal uremic models	Absence of calcification progression
Osteocalcin	No influence on the expression of	Absence of
Renin	Decreasing of protein expression <i>in vitro</i>	Positive influence on blood pressure and other renin-dependent functions

After replacing calcitriol to paricalcitol it was noted decrease of iPTH level from 901 pg/ml to 165 pg/ml and alkaline phosphatase from 280 IU to 65 IU by the end of treatment period. Despite the significant decrease of the iPTH, calcium and phosphorus levels in blood were not significantly changed, calcium level changed from 9.4 mg/dl to 9.7 mg/dl ($p=0.86$), and phosphorus from 6.1 mg/dl to 5.8 mg/dl ($p=0.77$).

In a cohort study [6], which included 67,399 dialysis patients with SHPT, the level of mortality among patients treated with paricalcitol was lower than among patients treated with calcitriol, 3.417/19.031 person-years and 6.805/30.471 person-years ($p<0.001$) respectively. In an analysis using Kaplan-Meier method, a higher survival rate was also noted among patients receiving paricalcitol ($p<0.001$). In this case, the more higher two-year survival rate observed among patients switched from calcitriol to paricalcitol in compare with patients switched from paricalcitol to calcitriol (73% vs. 64%, $p=0.04$). In retrospective cohort study involving 2,711 patients with SHPT on regular HD estimated the number of parathyroidectomies depending on therapy with paricalcitol or cinacalcet. The Cox model for proportional hazards, which has been adapted for age, sex, obesity, comorbidities, HD duration and the observation period, showed the reduce of the corrected risk by 83% (hazard ratio=0.17, $p<0.001$) in the group treated with paricalcitol in compare with patients receiving cinacalcet [7].

Data based on the three prospective, randomized, multicenter studies indicate effective suppression of iPTH secretion by paricalcitol, as well as the decrease in activity of bone isoenzyme of alkaline phosphatase and osteocalcin level in blood serum, due to reducing bone resorption [9]. Multivariate comparative analysis of the impact of therapy on the total number of days of hospital stay and the risk of first hospitalization after initiation of SHPT treatment with paricalcitol or calcitriol showed a reduced risk of the first hospitalization by 14% and the number of days' stay in the hospital by 6.84 per year among patients treated with

paricalcitol [9]. Serum concentrations of calcium and phosphorus in patients treated with paricalcitol did not differ from patients in the placebo group [5]. Results of placebo-controlled studies [1, 2] in groups of patients with CKD treated with placebo and paricalcitol showed that frequency of occurrence of the adverse events did not differ significantly. Four additional pharmaco-economic studies conducted in Europe and the US suggested that intravenous administration of paricalcitol is preferable in terms of price and quality, over calcitriol and alfacalcidol, in view of reducing the incidence of hospitalization and increasing the survival rate [10, 11, 12].

Conclusion

Thus, our results besides the results of international trials demonstrate the high efficacy of vitamin D receptors selective activator – paricalcitol in therapy of SHPT in patients with CKD, including patients treated with regular HD. The drug is effective reduces the iPTH level without affecting the calcium and phosphorus levels. In dialysis patients with SHPT treated with paricalcitol, a two-year survival was significantly higher than in patients with the calcitriol treatment ($p<0.001$).

Administration of paricalcitol to patients in predialysis stages of CKD with SHPT leads to not only normalization of iPTH and alkaline phosphatase levels, but to significant decrease of proteinuria level and regression of LVH and CHF. However, the cardioprotective and antiproteinuric effects of paricalcitol were not depending on the production of PTH. Paricalcitol selectively effects to the expression of genes of cell proliferation and differentiation regulators and molecular mediators of angiogenesis. The results of these studies hold the promise for widespread use of paricalcitol not only for treatment of SHPT in patients on HD, but also for nephro- and cardioprotection in CKD patients.

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