THE PLACE OF PARICALCITOL IN NEPHROPROTECTIVE STRATEGY OF PREDIALYSIS CHRONIC KIDNEY DISEASE DUE TO SYSTEMIC DISEASES

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Abstract

Nephroprotective strategy for the predialysis stages of chronic kidney disease (CKD) is aimed the maximum reduction of proteinuria (microalbuminuria) and the simultaneous normalization of hypertension as the most weighty of glomerulosclerosis progression factors. Among the lowering proteinuria means the early systematic calcitriol use in combination with renin-angiotensin system (RAS) blockers, erythropoietin and lipid-lowering drugs plays an especially important role.

The aim of the study

was a comparative analysis of calcitriol and paricalcitol effects to proteinuria reduce and secondary hyperparathyroidism (SHPT) development prevention in patients with systemic diseases and III–IV CKD stage.

Patients and methods

The study included 50 patients with CKD stage III–IV due to systemic diseases (35 systemic lupus erythematosus and 15 different forms of systemic vasculitis), which were divided into 2 groups. The 1 st group consisted of 28 patients (8 to III and 20 IV stage, which was used calcitriol at a dose of 0.25 mcg/day. In group 2 included 22 patients (9 with III and 13 with IV stage), they were administered paricalcitol 1 mg per day.

Calcitriol and paricalcitol with nephroprotective aim applied when the level of the blood intact parathyroid hormone (iPTH) was not below 65 pg/ml, and based on indicators of phosphor-calcium exchange. The 1 st and 2 nd groups' patients were required to appoint RAS blockers, erythropoietin with iron preparations, and statins. In 11 patients of group 1 and 12 patients in group 2 at admission and at the end of the study period Doppler ultrasound of common carotid arteries was performed.

Results

Prior to calcitriol and paricalcitol treatment, proteinuria was 1,3±0,5 g/day in group 1 and 1,2±0,3 g/day in group 2, and the level of PTH, respectively, – 76±18, 6 pg/ml and 82±16,6 g/ml. Combined calcification/atherosclerosis lesion of common carotid arteries was detected in 27,3% patients in group 1 and 33,3% in group 2. Calcitriol and paricalcitol were tolerated satisfactorily.

As a result, after 3 months from the beginning of these drugs use in patients with initially diagnosed increased PTH levels in the blood was reached the normalization of its content.

Reducing proteinuria occurred more rapidly ($p < 0,05$), while reducing hypertension by the end of 3 months was more significant ($p < 0,01$) in patients received paricalcitol, than with calcitriol.

During the same period among 12 patients in group 2 at 4 with diagnosed arteriosclerosis/calcification, episodes the hypercalcemia, as well as the progression of atherosclerosis/calcification were not identified. In contrast, among patients treated with calcitriol episodes of hypercalcemia were recorded at 27,3%, while in 3 patients with diagnosed during the screening arteriosclerosis/calcification were observed its progression

Conclusion

Application of paricalcitol at the predialysis stage of CKD due to systemic disease with hyperparathyroidism accompanied not only normal levels of PTH, but also a significant decrease in daily proteinuria and hypertension.

Keywords

chronic kidney disease, hemodialysis, secondary giperparatireoidism, parathyroid hormone, proteinuria, paricalcitol.

BACKGROUND

Nephroprotective strategy for the predialysis stages of chronic kidney disease (CKD) is aimed the maximum reduction of proteinuria (microalbuminuria) and the normalization of hypertension as the most

weighty factors of glomerulosclerosis progression. Early systematic use of calcitriol in combination with blockers of the renin-angiotensin system (RAS), an erythropoietin drugs and lipid-lowering drugs among the lowering proteinuria means plays an especially important role.

The final aim is to reduce mortality in patients with CKD from terminal uremia, including complications of renal replacement therapy (RRT), and the extrarenal manifestations of CKD in the first place - from heart disease morbidity.

Disorders of vitamin D homeostasis in CKD is detected at an early stage of renal failure. The majority of patients with CKD in stage III has the relative deficiency of the vitamin D_3 active metabolite – calcitriol (1,25 $(OH)_2D_3$) in the blood. In the future, as the deterioration of renal function when the level of glomerular filtration rate (GFR) falls below 50 ml/min/1,73 m^2 in children and below 30 ml/min/1,73 m^2 in adults, an absolute calcitriol deficit develops.

CKD progression is accompanied by a decrease in the number of vitamin D receptors (VDR) and calcium sensitive receptors (CaR) of parathyroid glands with a drop of parathyroid glands sensitivity to the action of calcitriol and Ca^{2+}.

Vitamin D levels in the blood may be low in CKD patients with nephrotic proteinuria, due to loss of 25 (OH) D_3 in the urine [1, 2].

Calcitriol inhibits paratireoid gland activity, causing a decrease in transcription and synthesis of PTH, increases the sensitivity of CaR in paratireoid gland cells, thereby blocking the mechanisms of secondary hyperparathyroidism development. In experimental studies have been shown that calcitriol deficiency may initiate of secondary hyperparathyroidism even in the absence of hypocalcemia [1, 2].

There is now evidence that the beneficial effects of calcitriol in the kidney due to an increase expression in proximal tubules of the renoprotective Klotho protein transmembrane form. [3–5]. But, as has been shown in clinical studies, intake of calcitriol is accompanied by a number of side effects:

- due to the calcium and phosphorus gastrointestinal absorption increase, rising their concentration in blood serum, which can advance the soft tissues calcification, including heart and blood vessels
- pharmacological calcitriol doses can cause damage to the vessels elastic membrane, causing inflammation
- excessive PTH suppression may transform secondary hyperparathyroidism in adynamic skeletal disease

To date, the only drug from the group of vitamin D, responsible to nefroprotective strategies, as well as prevention and treatment of secondary gyperparatireoidism is paricalcitol (Zemplar) – 1,25 $(OH)_2D_2$ – selective active metabolite of vitamin D, whose structure is modified of the side chain (D_2) and ring A. Paricalcitol selectively induces the expression of VDR (S-VDRA) genes in paratireoid glands by suppressing of IPTG secretion, do not activates of VDR in the intestine and has little effect on bone resorption, and therefore less likely causes hypercalcemia than non-selective active metabolite of vitamin D [1]. In contrast to calcimimetic group paricalcitol has expressive pleiotropic effects, due to of which risk of cardiovascular events, cancer reduces [11].

There are two formulations of the drug - a capsule for 1, 2 and 4 mcg and ampoule for 1 ml (5 micrograms). Capsules are indicated for the prevention and treatment of secondary hyperparathyroidism that develops in CKD III, IV and V stages, and ampoule - in CKD stage V [2, 6].

PATIENTS AND METHODS

The study included 50 patients with CKD stage III–IV. Patients were divided into 2 groups. The 1st group consisted of 28 patients (8 – with III and 20 – with stage IV), which was used calcitriol at the dose of 0.25 mcg/day. 22 patients (9 with III and 13 – stage IV) were included in group 2 and administered paricalcitol at a dose 1 mcg per day (tabl. 1). Calcitriol and paricalcitol with nephroprotective aim were applied when the blood level of intact parathyroid hormone (iPTH) was not below 65 pg/ml, and based on the indicators of phosphorus-calcium exchanges. The 1st and 2nd patients groups administered necessary RAS blockers, erythropoietin and iron preparations, and statins also. In 10 patients of group 1 and 12 patients of group 2 at admission and at the end of the study period common carotid arteries Doppler ultrasound was performed.

RESULTS

Prior to calcitriol and paricalcitol treatment, proteinuria was 1,3 ± 0,5 g/day in group 1 and 1,2±0,3 g/day in group 2, and the PTH level – 76±18, 6 pg/ml and 82 ± 16,6 pg/ml respectively (tabl. 2).

Combined calcification/atherosclerosis lesion of common carotid arteries was showed in 27,3% of group 1 patients and in 33,3% of group 2 patients. Calcitriol and paricalcitol were tolerated satisfactorily. As a result, after 3 months from the beginning of these drugs use, in initially diagnosed blood increased PTH levels patients the normalization of its contents was reached. In patients received paricalcitol, proteinuria

reducing occurred more rapidly (p <0,05), while hypertension reducing to the end of 3 months was more significant (p <0,01), than with calcitriol (tabl. 3).

Table1. *Distributionof patients according to stage of CKD*

Patients groups	CKD III st. (GFR* 30–59 ml/min/1,73 m²)	CKD IV st. (GFR 15–29 ml/min/1,73 m²)
group 1, n=28 Calcitriol (0.25 mcg/day, orally)	8	20
group 2, n=22 Paricaltsitol 1 mcg/day, orally)	9	13
altogether	17	33
in total	50	

** – GFR – glomerular filtration rate*

Table 2. *Effect of calcitriol and paricalcitol treatment on the concentration of IPTG in blood and daily proteinuria in patients with CKD IIII–IV stages due to systemic diseases*

Index	1 group		2 group	
	before treatment	after 6 months of calcitriol treatment (0,25 mcg/day)	before treatment	after 6 months of paricalcitol treatment (1 mcg/day)
iPTG (pg/ml)	76+18,6	66+12,2	82+16,6	60+14,4*
Proteinuria (g/day)	1,3+0,5	0,8+0,32	1,2+0,3	0,3+0,21*

*The differences were statistically significant: * – p < 0,05*

Table 3. *Comparative analysis of the blood pressure control effectiveness with use of ACE inhibitor (monopril) in combination with calcitriol or paricalcitol on LVMI regression*

Index	Δ Arterial pressure (mm Hg)		Δ Left ventricular mass index	
	systolic	diastolic	men	women
Monopril + calcitriol (0,25 mcg/day)	(-) 20,1+2,89	(-) 11,9+1,82	(-) 6,6+3,14	(-) 5,9+3,58
Monopril + paricalcitol (1 mcg/day)	(-) 23,3+3,21	(-) 12,8+2,03	(-) 20,6+4,25**	(-) 21,3+3,86**

*The differences were statistically significant: * – p < 0,01*

During the same period among 12 patients in group 2 at 4 with diagnosed arteriosclerosis/calcification, episodes of hypercalcemia, as well as the progression of atherosclerosis/calcification were not identified. In contrast, among patients treated with calcitriol, hypercalcemia episodes were recorded in 21,4% and in 3 diagnosed of arteriosclerosis/calcification patients during the screening was revealed its progression (tabl. 4).

Table 4. *The frequency of arterial calcification in patients with CKD stage III–IV, depending on the previous therapy*

Treatment	The frequency of atherosclerosis/calcification progression in%	
	CKD III st.(GFR 30–59 ml/min/1,73 m²)	CKD IV st.(GFR 15–29 ml/min/1,73 m²)
Calcitriol (0,25 mcg/day)	12,5%	15%
Paricalcitol (1 mcg/day)	0%	0%

DISCUSSION

Antiproteinuric effect of paricalcitol was confirmed in 3 double-blind, randomized, placebo-controlled studies including 220 patients with CKD III–IV stages and hyperparathyroidism. By the end of 24 weeks, proteinuria reduction was observed in 51% of patients treated with paricalcitol and 25% of patients receiving placebo (p=0,004). Antiproteinuric effect of paricalcitol was independent of patients' age, sex, race, whether they have concomitant diseases (diabetes, hypertension) [2]. Reduction of PTH level by 30% was noted in 91% of paricalcitol treated patients, compared with 13% of patients receiving placebo (p<0,001). At this reduced level of IPTG <110 pg/ml was observed in 75% of patients in the group treated with paricalcitol and 12% in the placebo group [1].

It is established, paricalcitol corrects intraglomerular hypertension by inhibiting of RAS, decreases the synthesis of renin, ET-1 receptors and inhibits of mesangial cell proliferation, podocite hypertrophy, and increases of megalin and nefrin expression. When paricalcitol combined with losartan achieved the most pronounced nefroprotective effect. Repeated morphological study of kidneys at 6 months of treatment was revealed slowing development of glomerulosclerosis and tubulointerstitial fibrosis. The high efficiency of this combination is explained by a more pronounced decline prorenin in blood with suppressed of its cellular receptors expression, as well as paricalcitol immunomodulatory effects on T-lymphocytes [1].

The experiment provided evidence that paricalcitol increases the expression of Klotho in kidney [4, 5]. Therefore, the paricalcitol use in CKD can be effective for inhibiting of renal disease progression. However, further clinical investigations require to confirm this hypothesis

Cardioprotective effect of paricalcitol shows LVH and heart failure regression leading to reduce of mortality in CKD predialisis and on regular hemodialysis (GD) stages. In the retrospective 3-year analysis of paricalcitol treatment outcomes of 67 000 dialysis patients, survival rate was 16% higher when compared with calcitriol treated patients [6, 7]. Indicated improvement of survival rate did not correlate with the duration of GD sessions, not depend on the level of calcium, phosphate and lipids and was mainly related to the more rapid suppression of PTH secretion, the molecular mechanisms of arteries calcification, inhibition of the RAS, reduced expression of proinflammatory cytokines in the myocardium and vascular endothelium by paricalcitol. [8–10].

High efficiency of perindopril and indapamide MB combination has been demonstrated in 4-year multicenter ADVANCE study in the group, which included more than 11,000 patients with insulin independent diabetes mellitus with use of severe hypertension and glycemic control [8]. In this case there was a significant decrease in total and cardiovascular mortality, and complications caused by micro- and macroangiopathy The incidence of microalbuminuria (proteinuria) and the progression of CKD decreased more than 20%. To enhance the antiproteinuric effect the authors recommend a combination of ACE inhibitor + indapamide MB + statin + epoetin + paricalcitol.

Paricalcitol with nefroprotective aim must be appointed at the level of intact blood PTH is not below 65 pg/ml, and based on indicators of phosphorus-calcium exchange [10].

Data based on three prospective, randomized, multicentral trials show the effective suppression of IPTG secretion by paricalcitol, as well as reducing of the bone alkaline phosphatase isoenzyme activity and osteocalcin content in the serum, due to reduced bone resorption [11–14].

Serum concentrations of calcium and phosphorus due to paricalcitol using did not differ from those in the placebo group [7].

As the results of the placebo-controlled studies [1, 2, 7] the frequency of adverse events in groups of CKD patients treated with placebo and paricalcitol did not differ significantly (table 5).

Thus, the use of paricalcitol in predialysis CKD stages with hyperparathyroidism is associated not only with normalization of IPTG and alkaline phosphatase, but also a significant decrease in daily proteinuria, and LVH and chronic heart failure (CHF) regression. At the same cardioprotective and antiproteinuric effects of paricalcitol do not depend on the PTH production [14]. Paricalcitol (Zemplar) selectively affects the gene expression of cell proliferation and differentiation regulators, molecular angiogenesis mediators.

Table 5. *Comparative analysis of the complications frequency in patients with CKD group when paricalcitol and placebo applying (summarized results of the placebo-controlled trials)*

Adverse events	Paricalcitol (n=62) %	Placebo (n=51) %
Common symptoms:		
Chill	5	2
Malaise	3	0
Fever	5	2
Flu-like symptoms	5	4
Edema	17	10
Circulatory system:		
Tachycardia	13	10
Digestive system:		
Dry mouth	3	2
Nausea	13	10
Vomiting	8	6
Aggravation of peptic ulcers	5	2
Nervous system:		
Dizziness	5	2

The results of research offers promise for wider use of paricalcitol (Zemplar) drug, not only for the treatment of secondary giperparatireoidism in dialysis patients but for nephro-and cardioprotection in patients with CKD.

CONCLUSION

The application of paricalcitol at the predialysis stage of CKD with hyperparathyroidism is accompanied not only with normal levels of PTH, but also a significant decrease in daily proteinuria and hypertension.

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