Kronik Böbrek Yetersizliğinde Dipiridamol Kullanımı PTH Direncini Artırabilir

Dipyridamole Can Augment the Resistance to Parathormone in Chronic Renal Failure

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ÖZET

Vazodilatör olarak kullanılan dipiridamol renal fosfat geri emilimini artırabilir. Bu çalışmada, stabil renal fonksiyonlu prediyaliz dönemindeki hastalarda dipiridamolün Ca, P metabolizması, PTH, renal fonksiyonlar ve elektrolitler üzerindeki etkilerini araştırmayı amaçladık.

Stabil renal fonksiyonlu, prediyaliz dönemindeki 30 olgu aldıkları ilaçlar ve diyetleri değiştirilmeden çalışmaya dahil edildi. Olguların tedavi öncesi (I) serum BUN, kreatinin, sodyum, potasyum, klor, Ca, P, magnezyum, PTH, Vitamin D3, kreatinin klirensi, idrar BUN, Cr, Na, FENa, Ca, P ve total fosfat reabsorpsiyonu değerlendirildi. Bu parametrelere 4 haftalık dipiridamol tedavisi sonrası (II) ve ilaç kesildikten 4 hafta sonra (III) tekrar bakıldı. Her 3 ölçümde PTH dışındaki parametrelerde farklılık yoktu. PTH için I, II ve III. ölçümlerde ortalama değerler sırası ile 152.2±124.1, 230.7±196.6, 210.9±163.2 pg/mL idi. PTH I-II ve I-III arasındaki farklılıklar anlamlı idi ($p<0.05$). Fakat, II ve III. ölçümler arasındaki farklılık anlamlı değildi.

Sonuç olarak, dipiridamol renal fonksiyonlar, serum Ca, P ve Vitamin D3 düzeylerini değiştirmeden serum PTH düzeylerini artırmıştır. Bu etki dipiridamol kesildikten sonraki 4 hafta süresince devam etmiştir. Dipiridamolün PTH üzerindeki bu etkisi sekonder hiperparatiroidili olgularda incelenmeli ve prediyaliz dönemdeki hastalarda dikkatli kullanılmalıdır.

Anahtar sözcükler: dipiridamol, PTH, böbrek yetersizliği

ABSTRACT

Dipyridamole which is used for vasodilatation might enhance renal tubular reabsorption of phosphate. In this study, we aimed to investigate the effect of dipyridamole on Ca, P metabolism, PTH, renal functions and electrolytes in pre-dialysis patients with stable renal function.

Thirty pre-dialysis patients with stable renal function were treated with dipyridamole for 4 weeks without their treatment and diet being changed. Baseline (I) serum levels of BUN, creatinine, sodium, potassium, chlorur, Ca, P, magnesium, PTH, Vitamin D3, creatinine clearance and urinary BUN, Cr, Na, FENa, Ca, P, total phosphate reabsorption were measured. These parameters were repeated at the end of the therapy (II) and 4 weeks after withdrawal of dipyridamole (III). There was no difference for all parameters for 3 measurements, except PTH. The mean values of PTH for I, II and III measurements were 152.2±124.1, 230.7±196.6, 210.9±163.2 pg/mL, respectively. The differences between I-II and I-III for PTH were significant ($p<0.05$). But, the difference between II and III was not significant.

Consequently, dipyridamole increased serum PTH levels without any effect on renal functions, serum Ca-P and Vitamin D3 levels and this effect continued for 4 weeks after withdrawal of dipyridamole in pre-dialysis patients . But, this effect of dipyridamole on PTH should be investigated in patients with secondary hyperparathyroidism and we recommend being cautious in using of dipyridamole in predialysis patients.

Keywords: dipyridamole, PTH, renal failure

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Introduction

Disturbances in calcium (Ca) and phosphorus (P) metabolism occur in patients with chronic renal failure. Secondary hyperparathyroidism (HPT) is an important factor for morbidity and mortality in renal disease. Hyperphosphatemia, hypocalcemia and HPT are common findings in advanced renal failure and they usually become evident when the GFR shrink from normal values to 30 mL/min. Several factors may affect the levels of serum Ca, P and PTH in patients with renal failure (1). Dipyridamole is used for vasodilatation and anti-aggregation. In literature, there are a few studies reporting that dipyridamole

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might enhance renal tubular reabsorption of phosphate (2,3).

In this study, we investigated the effect of dipyridamole on serum and urinary Ca and P, PTH, renal functions and electrolytes in pre-dialysis patients with stable renal function. According to our knowledge, this is the first report about the effect of dipyridamole on PTH in pre-dialysis patients.

Material and Methods

Forty-three pre-dialysis patients with stable renal function were included in the study. The subjects did not change their treatments and habitual diets. After taking their oral approval, the patients were treated with dipyridamole 75 mg three times a day for 4 weeks. At the end of the study period, dipyridamole was stopped.

Due to dipyridamole related nausea/vomiting, three of 43 patients could not complete the study and 10 patients did not come to follow-up. So, thirty patients were assessed. The causes of renal failure were hypertensive nephrosclerosis (n=6), diabetic nephropathy (n=7), chronic glomerulonephritis (n=8), tubulointerstitial nephritis (n=2), amyloidosis (n=1), systemic lupus erythematosus (n=1) and unknown etiology (n=5). Only three patients were taking diuretics and the others were not using drugs which may affect (Vitamin D_3, P binding drugs, anti-convulsive drugs, allopurinol or oral P) Ca and P metabolism.

Before dipyridamole (I) serum levels of glucose, lipids, uric acid, BUN, creatinine (Cr), sodium (Na), potassium (K), chlorur (Cl), Ca, P, magnesium (Mg), AST, ALT, GGT, PTH, Vitamin D_3, creatinine clearance (Ccr) and urinary BUN, Cr, uric acid, Na, FE_{Na}, Ca, P, total phosphate reabsorption (TPR) were measured. Vitamin D_3 was assessed by radioimmunoassay method and PTH was analyzed by immunoassay with ELECSYS E 170 kit. Other parameters were evaluated by standard methods. These measurements were repeated twice, at the 4th week of dipyridamole treatment (II) and 4 weeks after the withdrawal from dipyridamole (III).

TPR, FE_{Na}, Ccr, were calculated by using the following formulas; TPR= 1-UPO4×Scr/Ucr×SPO4, FE_{Na}= UNa×Pcr/ PNa×Ucr×100, Ccr= Ucr×Uv/Pcr×1440. Re-

Table I. The levels of BUN, creatinine, creatinine clearance, electrolytes, Ca, P, uric acid, PTH, Vit D3, FNaE and TPR

Serum	Measurement I	Measurement II	Measurement III	P value (for all)
BUN (mg/dL)	40.68±16.6	40.00±18.71	41.12±19.00	>0.05
Creatinine (mg/dL)	2.80±1.26	2.80±1.35	2.86±1.57	>0.05
Na (mEq)	139.08±3.42	138.40±5.98	138.64±4.70	>0.05
K (mEq)	4.69±0.37	4.84±0.43	4.70±0.46	>0.05
Ca (mg/dL)	9.57±0.51	9.42±0.75	9.46±0.44	>0.05
P (mg/dL)	3.97±1.06	4.14±0.85	4.31±1.07	>0.05
PTH (ng/mL)	152.2±124.1	230.7±196.6	210.9±163.2	<0.05*
Vit D3 (ng/mL)	29.09±12.40	30.61±8.70	27.91±8.77	>0.05
Uric acid (mg/dL)	7.60±1.29	7.58±1.50	7.23±1.48	>0.05
Urinary				
Nitrogen (mg/day)	7293±2221	6635±2101	6117±2489	>0.05
Creatinine (mg/day)	1017±374.7	983.8±407.3	924.8±418.8	>0.05
Creatinine clearance (mL/min)	32.78±36.67	32.29±19.83	32.02±23.13	>0.05
Uric acid (mg/day)	410.7±149.7	383.5±161.0	353.3±169.2	>0.05
Na (mEq/day)	158.4±101.0	144.2±75.4	136.0±83.8	>0.05
K (mEq/day)	45.42±26.80	40.00±17.40	36.27±16.90	>0.05
Ca (mg/day)	58.72±44.86	53.90±54.40	51.88±50.04	>0.05
P (mg/day)	503.8±198.5	461.0±213.1	429.3±217.1	>0.05
FENa	2.76±1.64	2.61±1.42	2.49±1.22	>0.05
TPR	0.63±0.15	0.68±0.18	0.67±0.16	>0.05

peated measurement test was used for statistical analysis.

Results

Of the 43 subjects, 30 patients (14 male, 16 female) completed the study. The mean age of males was 49.38±15.46 years; the mean age of females was 50.14±17.96 years. The patients were between stage 2 to stage 5 kidney disease according to National Kidney Foundation (NKF). At baseline (1), end of the dipyridamole treatment (2), and 4 weeks after wash-out period (3), for serum glucose, BUN, creatinine (Cr), Na, K, Cl, Mg, uric acid (UA), ALP, AST, ALT, GGT, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, albumin, there were no differences ($p>0.05$). The mean levels and significance of serum Ca, P, vit D_3, PTH and 24 hour urinary BUN, Cr, creatinine clearance (Ccr), UA, Na, K, Ca, P, FN_{AE} and TPR are shown in Table I and Figure 1. PTH levels are shown in Figure 2. Although 3 patients who were taking diuretics were excluded, the statistical results did not change.

Discussion

In this study, we did not find any difference in renal function, serum levels of Vit D_3, uric acid, Ca, P, serum and urinary electrolyte levels, FE_{Na}, TPR, between baseline (I) and after 4 weeks of dipyridamole treatment (II), whereas, serum PTH I and II, I and III levels were different and increase of PTH persisted after 4 weeks of withdrawal of dipyridamole.

In recent years, PTH has been accepted as a polyhormone biological activity of which has been mediated with multiple fragments on multiple receptors (4). PTH stimulating factors are P retention, hypocalcemia, Vitamin D deficiency, decreased and/or insensitivity of Vitamin D receptors (VDRs) and Ca^{+2} sensing receptors (CaSRs) (1). Renal function tests, serum Ca, P, TPR, urinary P excretion and Vitamin D_3 levels were similar before and after dipyridamole treatment. According to these data, we cannot explain easily the increase in PTH levels with dipyridamole in our study. But, PTH might be stimulated by dipyridamole related to change in VDRs and/or CaSRs gene expression. Although serum PTH levels increased in our study, unchanged serum levels of Ca, P, Mg, and Vitamin D_3 may be explained with resistance to the peripheric effect of PTH. A study has shown that addition of uremic filtrate into cell cultures may desensitize PTH-adenylate cyclase activity and induce resistance to PTH (5). In our patients, increase of PTH might be the result of potential PTH resistance occuring secondary to dipyridamole. In literature, studies have demonstrated that PTH activates adenylate cyclase enzyme activity and its peripheric effects exist via cyclic adenosine monophosphate (cAMP) (6). The entering of adenosine which is substrate of intracellulare cAMP, is blocked by dipyridamole (7). In a study with platelets, adenosine caused accumulation of intracellular cAMP via interactions platelet A_{2A} receptors that is coupled with adenylate cyclase through G_S protein (8). As an inhibitor of adenosine reuptake, dipyridamole can decrease intracellular

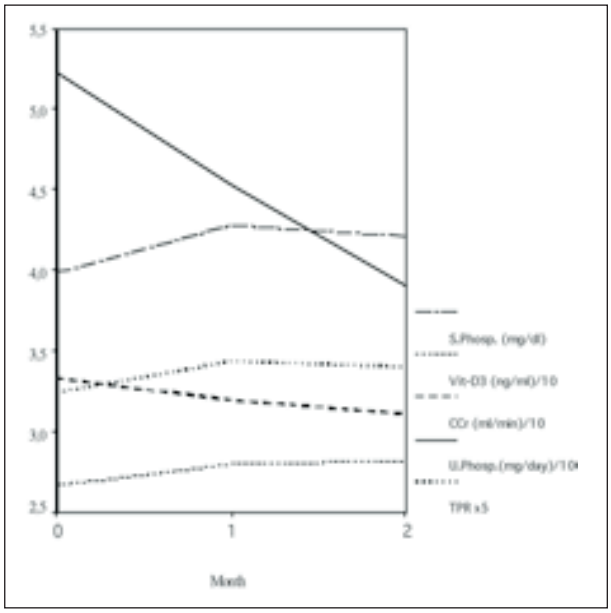

Figure 1. The values of P, Vit D3, Ccr and TPR.

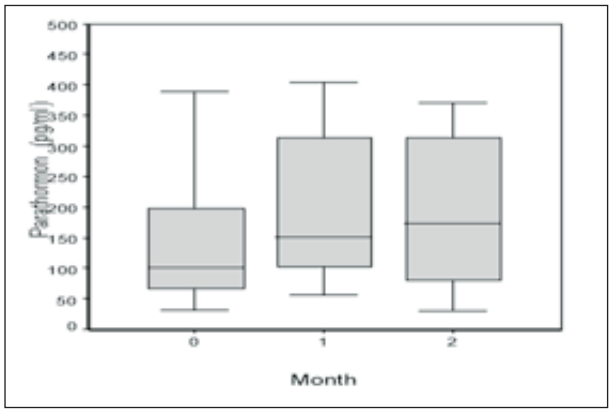

Figure 2. The PTH levels of the patients.

cAMP and cause a resistance to the peripheric effect of PTH.

In conclusion, the use of dipyridamole in patients with stable chronic renal failure increased serum PTH levels without any effect on renal functions, serum Ca-P and Vitamin D_3 levels and this effect continued for 4 weeks after withdrawal of dipyridamole. But, this effect of dipyridamole on PTH should be investigated in patients with secondary hyperparathyroidism and we recommend being cautious in using of dipyridamole in predialysis patients.

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