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KRONİK HEMODİYALİZ HASTALARINDA ARALIKLI ORAL VE İNTRAVENÖZ 1.25 $(OH)_2$ CHOLECALCIFEROL (CALCITRIOL) TEDAVİSİ

INTERMITTENT ORAL AND INTRAVENOUS 1.25 (OH), CHOLECALCIFEROL (CALCITRIOL) TREATMENT IN CHRONIC HEMODIALYSIS PATIENTS

Ş.Sindel, Ü.Derici, T.Arinsoy, M.Bali, H.Özdemir*, E.Hasanoğlu**

Gazi Üniversitesi Tıp Fakültesi Nefroloji Bilim Dalı,
* Radyoloji Anabilim Dalı, ** Pediatrik Nefroloji Bilim Dalı, ANKARA

ÖZET

Kronik hemodiyaliz (CHD) hastalarmdaki sekonder hiperparatiroidizm tedavisinde aralıklı intravenöz (IVC) ve oral calcitriol (ORC) uygulamasının etkili olduğu gösterilmiştir. Biz, 16 haftalık aralıklı intravenöz ve oral calcitriol tedavisiyle CHD hastalarmdaki paratiroid gland boyutları ve serum intakt-Parathormon (I-PTH) düzeylerinde olan değişimi incelendi. Calcitriol (lmikrogram/haftada 3 kez) her diyalizin sonunda verildi. Çalışma sonunda serum I-PTH düzeyleri IVC grubunda 235.5±58.3'den 138±54 pg/ml'ye, ORC grubunda ise 243.5±66.5'den 81.4+3 7.2pg/ml 'ye geriledi. Paratiroid gland boyutları ise her bir tedavi grubunda anlamlı bir değişim göstermedi. Bu çalışmada her iki tedavi şeklinin sekonder hiperparatiroidizm 'li CHD hastalarında serum I-PTH düzeylerini belirgin olarak azalttığı ancak bu PTH baskılayıcı etki açısından tedavi grupları arasında bir fark olmadığı sonucuna vardık. Bununla birlikte paratiroid glandların boyutlarında her iki tedavi yöntemiyle de herhangi bir gerileme gösterilemedi.

Anahtar kelimeler: Sekonder hiperparatiroidizm, calcitriol, aralıklı tedavi,

SUMMARY

Intermittent intravenous and oral Calcitriol have been shown to be effective in the treatment of secondary hyperparathyroidism in chronic hemodialysis (CHD) patients. We exomined the time course of serum levels of Intact Parathyroid Hormone (I-PTH) and size of parathyroid glands in CHD patients with intermittent oral (ORC, n=15) and intravenous calcitriol (IVC, n=17) therapy for 16 weeks. Calcitriol (1 microgram/3 timer per week) was given at the given at the end of each dialysis. At the end of the study, serum I-PTH levels decreased significantly from 235.5±58.3 to 138±54 pg/ml in IVC group and from 243.5±66.5 to 81.4+37.2 pg/ml in ORC group. On the other hand, parathyroid gland sizes remained constant after each treatment modalities. We concluded that both IVC and ORC tretments result in a significant decrement in serum levels of I-PTH in CHD patients with secondary hyperparathyroidism (Schpt); but there was no difference between IVC and ORC for the PTH suppressive-effect. However, no size reduction of parathyroid glands was demonstreated with both treatments.

Key Words: Secondary hiperparathyroidism, calcitriol, intermittent therapy, hemodialysis patients

INTRODUCTION

Renal osteodystrophy (RO), the term used to describe the skeletal complications of end-stage renal disease, is a multifactorial disorder of bone remodeling, and sekonder hiperparatiroidizm (Schpt) is one of its central features (1,2). The low levels of serum calcium and 1.25 $(OH)_2$ vitamin D, the high serum phosphate levels, abnormal parathyroid gland function and skeletal resistance to the calcemic action of PTH plays an important role in the genesis of hyperparathyroidism (1,3). Phosphorus also play a major role in regulating production of calcitriol by altering the activity of the enzyme Iα- hydroxylase. Thus, the syntesis of calcitriol decrease by the effects of phosphorus retention (3). In addition, a low-phosphorus diet may have an effect on the secretion of PTH (3,4,5). The mechanism of this

effect is not yet known. Silver et al (6). Using a primary culture of parathyroid cells showed that calcitriol reduced pre-pro PTH mRNA levels by 50 % in 48 hours. Moreover, Cantley et al (7) demonstrated that a reduction pre-pro PTH mRNA levels correlated with a similar reduction in PTH secretion. Other some investigators also demonstrated these similar results (1,3,8). Calcitriol has also a indirect effect on the syntesis and secretion of PTH by increasing serum calcium levels. The observations in parathyroid cells in vitro obtained from hyperplastic glands from uremic patients have indicated that the set point for calcium-regulated PTH secretion was shifted to the right. But, following the treatment of calcitriol, the set-point for calcium returned toward normal (3,9).

Oral and intravenous daily administration of calcitriol was used to cotrolled Schpt for a long time. But recently, intermittent calcitriol treatment modality was reported instead of daily administration, because of hypercalcemic effects and low response rate. Therefore, it suggested that serum PTH levels were markedly decreases with intermittent theraphy. We also performed a prospective and comperative protocol study and evaluated the effects of calcitriol administered intravenously or orally at the same doses and intervals between doses to suppress serum I-PTH and reduce parathyroid gland size in hemodialysis patients with Schpt.

PATIENTS AND METHODS

Thirty-two hemodialysis patients with end stage renal disease were selected to participate in the study. All patients had serum levels of I-PTH above the normal range and serum aluminum levels within normal. The underlying renal diseases were glomerulonephritis and pyelonephritis (n=23), diabetic nephropaty (n=2), amyloidosis (n=5), malign hypertension (n=2). None of the patients had received vitamin D within 3 months prior the study and none were taking anticonvulsants, steroids, or any other medications that might potentially interfere with mineral metabolism. This patients were dialyzed two or three times a week using cuprophan membrane, bicarbonate as a buffer and a dialysate Ca±+ concentration of 1.75 mMol/L. During the study period, phosphate binders containing aluminum and calcium were not used and to prevent hypercalcemia. Calcium supplementation was discontinued. According to the results of basal evaluation, the patients were divided into 2 groups. All patient's characteristics in both groups were demonstrated in **Table 1**.

Group 1 (IVC) received calcitriol intravenously (lmicrogram/three times per week) while group II (ORC) received the same doses at the end of each dialysis, but orally. Both groups were treated for 16 weeks. The following changes were planned in the protocol; in the case of hypercalemia (> 11.5 mg/dl) and/or Ca*P product of more than 70, calcitriol was suspended until serum calcium and Ca*P product were normal (Calcium-corrected for albumin **-<11.5** mg/dl, Ca*P<70). Total calcium, phosphorus, albumin and alkaline phosphatase were measured monthly by autoanalyzer (Technicon RA-XT, USA). All blood samples were drawn before each dialysis session. The I-PTH were measured before and at the end of the study

Table 1: Patient characteristics in both groups

	Group I (IVC)	**Group II (ORC)**	**P value**
n:	17	15	NS
Mean age ± SD (years)	50 ±3 (19-65)	53.8 ± 11.7(31-65)	0.46
Male: female	11:6	4:11	0.37
Mean dialysis duration (mo)	24.3 ±6.2	27.8 ±5.6	0.32
Dialysis number 2 times Per week 3 times Per week	 9 patients 8 patients	 8 patients 7 patients	 NS NS
I-PTH(n: 4.8-30.1 pg/ml)	235.5 ±58.3	243.5 ±66.5	0.86
Parathyroid gland volume (cm)	0.19 ±0.06	0.21 ±0.12	0.19
Total Ca++ (n:8.2-10.8 mg/dl)	8.3 ±0.23	9.4 ±0.29	0.0005
Phosphorus (n: 2.5-4.6 mg/dl)	5.7 ±0.3	5.8 ±0.43	0.81
ALP (n: 30-80 U/L)	**117.7** ± 15.65	117.1 ± 18.1	0.95
CaxP $(mg/dl)^2$	47.9 ± 3	53.4 ±3.81	0.23

by immunoradiametric assay (IRMA, Medgenix, Belgium). The sizes of parathyroid glands were measuder using an ultrasonografic transducer of 7 mHz with lineer probe (Hitachi EUB 515A, Tokyo, Japan).

STATISTICS

All parameters are presented as mean and SD, and P<0.05 used to indicate significance. Comparisons between treatments were carried out by the Mann-Whitney U test. Wilcoxon test was used to compare time related changes in the two groups. We used the Fisher's exact test to compare the episodes of hypercalcemia and hyperphosphatemia.

RESULTS

All the biochemical parameters before and after calcitriol treatment are summarized in **Table 2 and 3.** No difference of baseline parameters between I VC and ORC was found. Only, serum calcium levels were higher in the second group; but this levels were in the high normal range. Significant decreases of I-PTH were recognized after 16 weeks of both IVC and ORC treatment (PO.05). The maximal reduction of mean I-PTH were 41.4 % and 66.6 % during IVC and ORC treatment respectively. But the I-PTH suppressive effect was not significantly different between two groups (P=0.05, **Figure 1).** As shown in table 2 and 2, we observed no treatment effect to reduce either the average gland volume after 16 weeks of calcitriol administrations. In addition, there were no differencesbetween the intravenous and oral therapy groups with regard to gland volume (P=0.35, P=0.14, respectively) **(Figure** 2).

Table 2: Biochemical parameters before and after calcitriol treatment

	IVC			ORC		
	Before	**After**	**P value**	**Before**	**After**	**P value**
I-PTH(n:4.8-30.1 pg/ml)	235.5 ±58.3	138 ±54	0.03	243.5 ±66.5	**81.4 ±37.2**	0.001
Parathyroid gland volume (cm3)	0.19 ±0.006	0.12 ±0.03	0.35	0.21 ±0.12	0.25 ±0.19	0.14
Total calcium (8.2-10.8 mg/dl)	8.3 ±0.3	8.6 ±0.3	0.127	9.4 ±0.3	9.3 ±0.4	0.712
Phosphorus (2.5-4.6 mg/dl)	5.7 ±0.3	5.9 ±0.2	0.554	5.8 ±0.4	6.2 ± 1.2	0.334
ALP (30-80 IU/L)	**117.7** ± 15.7	**102.9** ± 17.9	0.214	**117.1 ± 18.1**	84.9 ± 11.6	0.032
Ca*P product	47.9 ±3	50.3 ±2.5	0.407	53.4 ±3.8	57.2 ±4.1	0.609
Hypercalcemic episodes/patients	-	7/7	-	-	8/6	
Hyperphosphatemic episodes/patients	–	19/10	–	–	10-6	

Table 3: Biochemical parameters of the groups after calcitriol treatment

	IVC-after treatment	**ORC-after treatment**	**P values**
I-PTH(n: 4.8-30.1 pg/ml)	138 ±54	81.4± 37.2	P=0.55
Parathyroid gland volume (cm3)	0.12 ±0.03	0.25 ±0.19	P=0.35
Total calcium (8.-10.8 mg/dl)	8.6 ±0.3	9.3 ±0.4	P=0.15
Phosphorus (2.5-4.6 mg/dl)	5.9 ±0.2	6.2 ± 1.2	P=0.49
ALP (30-80IU/L)	102.9 ± 17.8	84.9 ± 11.6	P= 0.82
Ca * P product	50.3 ±2.5	57.2 ±4.1	p=0.71
Hypercalemic episodes / patients	7/7	8/6	P= 0.76
Hyperphosphatemic episodes / patients	19/10	16/10	P= 0.92

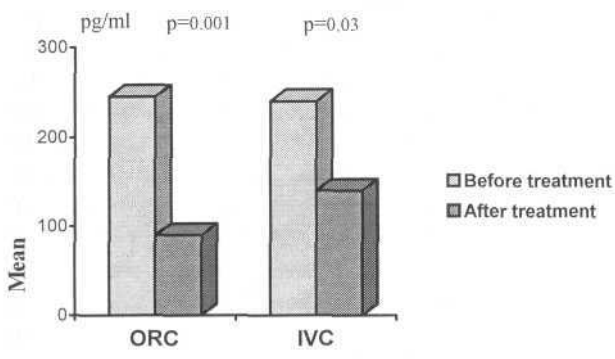

Figure 1: Changes in serum T-PTH levels following treatment with IV and Oral intermittent calcitriol for 16 weeks

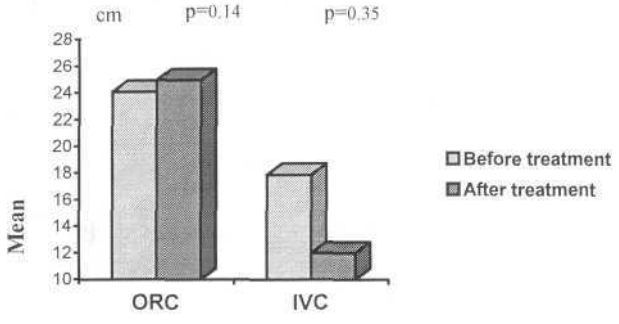

Figure 2: Effects of IV and oral therapy on parathyroid gland volume

Calcitriol administration was assosiated with a significant increase in serum total calcium in both groups. There were no significant differences in the number of episodes of hypercalcemia or hyperphosphatemia between treatments groups. Other prameters were not altered during IVC therapies, including serum phosphorus and alkaline phosphatase. But, the significant reduction in serum mean ALP levels occurred after 16 weeks ORC treatment (P=0.03).

DISCUSSION

Calcitriol and other vitamin D preparations (vitamin D, alfacalcitriol, dihydrotachysterol, and calcifediol) have been widely used to treat secondary hyperparathyroidism, as well as to correct deficient endogenous production of 1.25-dihydroxy-cholecalciferol. The present study also demonstrated that both intermittent intravenoous and oral calcitriol are effective in lowering serum I-PTH levels in chronic hemodialysis patients with Schpt. But there was not difference between IVC and ORC for the PTH suppressive effect. On the other hand, it was found that hypercalcemic and hyperphosphatemic episodes were similar in both treatment groupsm. Only serum means ALP levels decreased at the end of study period in group 2.

Recent uncontrolled clinical investigations suggest that attaining pharmacologic serum 1.25 (OH), vitamin D levels by administering calcitriol intravenously are more effective in suppressing serum PTH than orally administered calcitriol (9,10,11,12,13). These clinical trials propose that the intravenous route administration may be associated with fewer episodes of hypercalcemia than orally administered calcitriol and a higher bioviability and effect of the sterol can be expected after intravenous administration. On the other hand, other uncontrolled studies indicate that daily or intermittent oral administrations of calcitriol can also suppress serum PTH levels with few complications provided that sufficient amounts of calcitriol are given to attain physiologic serum 1.25 $(OH)_2$ vitamin D concentrations (14,15,16,17,18). Recently, intermittent oral or intravenous administrations of calcitriol have also been shown to be effective. In our study, intermittent low dose oral and intravenous administration of calcitriol were used and compared. In the other studies, eficacy of pulse IV and oral calcitriol therapy were also demonstrated. But in th calcitriol therapy was proposed (19,20). However, both hypercalcemia and hyperphosphatemia are still very important problems during therapy in our study.

It has been reported that calcitriol therapy decreases not only parathroid secretion but also parathroid hyperplasia, as has recently been shown in laboratory animals (21). But Quarles et al (22) and Fisher-Harris (23) did not observed any difference in the degree of parathyroid hyperplasia. In addition we observed similar to the recent findings no decrement in estimated gland volume or number in both oral and IV calcitriol treatment groups. The basis for this refractoriness is unclear but may represent a combination of increased functioning gland mass (diffuse hyperplasia and hypertrohy), a abnormalities related to vitamin D receptor deficiency, limited tolerance to high calcitriol dosage, altered calcium sensitivity in individual parathyroid cells and/or monoclonal growth of autonomous parathyroid secreting cells in some patients (18,24). In addition Fukuda et al (24) showed that the calcitriol receptor density is more reduced in nodular hyperplasia than is diffuse hyperplasia and thus be more resistant to calcitriol. In our study, these abnormalities and effects may be responsible for the refractoriness. Further studies are needed to define the mechanisms of this abnormalities and effects. In summary, intermittent oral and intermittent intravenous calcitriol have been shown to be effective in the treatment of Schpt in hemodialysis patients;but we found no advantage of one over the

other treatment modality with regard to efficacy. However, no sizes of parathyroid glands' reductions were demonstrated with two treatment modalities.

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