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ORAL PULSE CALCITRIOL THERAPY IN CHILDREN WITH RENAL OSTEODYSTROPHY

ÇOCUKLARDA RENAL OSTEODİSTROFİDE ORAL PULSE KALSİTRİOL TEDAVİSİ

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ABSTRACT

Objective: The aim of this study was to determine the effects and safety of oral pulse calcitriol therapy in patients with renal osteodystrophy (ROD) refractory to the conventional oral vitamin D therapy.

Materials and methods: After baseline determination of serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), urea, creatinine, intact parathyroid hormone (iPTH), osteocalcin, calcitriol levels and parathyroid gland ultrasonography, oral pulse calcitriol therapy was started at doses of 2 μg, three times a week, and all these parameters were followed up for a period of 4-6 months.

Results: Serum iPTH levels measured in the 2nd and 6th months were significantly lower than basal serum iPTH levels ($p<0.05$). Although basal and post-treatment serum osteocalcin and calcitriol levels were in the normal range, increment in serum calcitriol levels and decrement in serum osteocalcin levels were found statistically significant ($p<0.05$). The changes of serum Ca, P, CaxP levels were not found statistically significant during the study protocol; however, serum ALP levels declined significantly ($p<0.05$).

Conclusion: Our results indicate that oral pulse calcitriol therapy is well tolerated and this treatment can suppress iPTH levels without increasing hypercalcaemia risk in refractory secondary hyperparathyroidism in patients with chronic renal failure.

Key words: Renal osteodystrophy, calcitriol, pulse therapy, children

ÖZET

Amaç: Bu çalışmanın amacı, konvansiyonel oral D vitamini tedavisine dirençli renal osteodistrofili çocuklarda oral "pulse" kalsitriol tedavisinin etkinliğini değerlendirmekti.

Gereç ve yöntem: Bazal serum kalsiyum, fosfor, alkalen fosfataz, üre, kreatinin, intakt paratiroid hormon (iPTH), osteokalsin, kalsitriol düzeyleri için örnek alındıktan ve paratiroid bezi ultrasonografisi yapıldıktan sonra haftada üç kez, 2 μg oral pulse kalsitrioil tedavisi başlandı ve tüm parametreler 4-6 ay süreyle izlendi.

Bulgular: İkinci ve 6. ayda ölçülen serum iPTH düzeyleri bazal düzeye göre anlamlı olarak düştü ($p<0,05$). Bazal ve tedavi sonrası serum osteokalsin ve kalsitriol düzeyleri normal sınırlarda olmasına karşın, serum kalsitriol düzeyindeki artış, serum osteokalsin düzeyindeki azalma istatistiksel olarak anlamlıydı ($p<0,05$). Serum Ca, P, CaxP düzeylerindeki değişiklikler istatistiksel olarak anlamlı bulunmadı; ancak alkalen fosfataz düzeyi anlamlı olarak düştü ($p<0,05$).

Sonuç: Oral "pulse" kalsitriol tedavisi iyi tolere edilmektedir ve bu tedavi kronik böbrek yetersizliği olan sekonder hiperparatiroidizmli çocuklarda serum iPTH düzeyini hiperkalsemi riskine yol açmaksızın baskılayabilmektedir.

Anahtar kelimeler: Renal osteodistrofi, kalsitriol, "pulse" tedavi, çocuk

INTRODUCTION

Life expectancy and life quality of chronic renal failure patients have increased after the application of successful renal replacement and medical therapy methods in clinical use. Consequently, protection against bone disease and treatment of osteodystrophy have become more important (3, 5, 10).

Since 1950's, metabolic complications were unavoidable with vitamin D analogs in the treatment of renal osteodystrophy (ROD). Thus, clinicians looked for new treatment methods which might suppress serum parathyroid hormone (PTH) without causing hypercalcemia (3, 5, 10). In 1984, Slatopolsky et al. (14) used IV calcitriol therapy

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in haemodialysis (HD) patients and showed that PTH levels were suppressed without increasing hypercalcemia risk. From then on, this new therapy has been used commonly. Later, in Japan, Tsukomoto et al. (16) came up with similar results in calcitriol oral pulse therapy. Oral and IV calcitriol pulse protocols were matched in many adult studies, but ultimately it has been accepted that using calcitriol therapy by "pulse" method was more significant than the route of the therapy (3, 7, 8, 11-13, 15, 17, 18). In some studies in which IV pulse calcitriol therapy was used, serum osteocalcin levels were investigated and different results with this bone protein were reported (1, 8, 9).

We analyzed the effects and safety of oral pulse calcitriol therapy in children with secondary hyperparathyroidism (HPT) refractory to the conventional oral vitamin D therapy. Pre-treatment and post-treatment serum osteocalcin levels were also measured.

MATERIALS and METHODS

Approval of the local ethical committee was obtained for the study. Ten patients (6 females, 4 males) with chronic renal failure were included in the study. The mean age of the patients was 13.7 ± 2.3 (9.9 – 16.6 years of age). The primary renal diseases and other characteristics of the study group are shown in Table 1. Four patients were on HD treatment and in all of them, 2.5 mEq/L Ca^{++} containing dialysates were used. At the beginning of the study pre-treatment oral Ca^{++} salt dosages were not changed. According to serum levels of calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), calciumxphosphorus (CaxP), and intact parathyroid hormone (iPTH), the dosage of oral Ca^{++} salt was modified. In patient six, these changes did not enable to modify the Ca, P equilibrium and it was necessitated to change the calcitriol dosage. During the study period, aluminum (Al) and magnesium (Mg) salts as phosphate binders were not used. There had been no patient withdrawn due to drug dependent problems. After baseline determination of serum Ca, P, ALP, urea, creatinine, iPTH, osteocalcin, calcitriol levels and parathyroid gland ultrasonography (US), oral pulse calcitriol therapy was started at doses of 2 μg, three times a week, regardless of the patients' weights. HD patients received the same doses after each HD session. All patients were followed up for 4 months, but protocol was extended to six months in six patients to evaluate the effectiveness of these different periods on PTH supression. Serum iPTH levels below 2.5 times of normal levels were accepted as a good control for secondary hyperparathyroidism (HPT). Serum Ca, P, ALP were measured weekly during the first month, every 2 weeks during the second month and once a month until the end of the study. Serum PTH was measured before treatment, and in the 1st, 2nd and 4th months; serum osteocalcin and calcitriol were measured before and after treatment. In six patients for whom protocol was extended to six months, serum iPTH level measurements were reevaluated in the 6th month. Changes in the pre-treatment and post-treatment values were analyzed for the same patient.

Serum Ca, P, ALP, urea, creatinine levels were determined by using autoanalyzer. Intact PTH and osteocalcin levels were measured by IRMA technique and calcitriol was measured by radioreceptor assay. Parathyroid gland US was done by Acuson 128-XP/10 instrument (Soma Technology Inc., Cheshire, CT, USA).

Statistical analysis was performed using Wilcoxon test, Mann-Whitney-U test and Pearson correlation test. "P" values less than 0.05 were accepted as statistically significant.

RESULTS

Serum intact parathyroid hormone (iPTH) levels measured in the 2nd and 6th months were significantly lower than basal serum iPTH levels ($p<0.05$), but there were no statistically significant differences between the basal and 4th month serum levels (in the 4th month measurements, an unexpected serum PTH level increment was observed in patient one, if this measurement is excepted, also there were significant differences between basal and 4th month

Table 1. Characteristics of the study group

No	Age (years)	Sex	Primary disease	Age at diagnosis	Duration of CRF	Duration of dialysis
1	9.9	Male	Urolithiasis	5 years	4.5 years	9 months
2	10.8	Female	Unknown	10 years	?	-
3	11.10	Female	Unknown	7 years	5 years	-
4	13	Male	VUR nephropathy	1 year	7 years	2.5 years
5	14	Female	Bilateral ureteral valve	2 years	5 years	-
6	15	Female	Toxicity of chemotherapy	11 years	4 years	-
7	15.3	Male	Posterior urethral valve	9 years	6 years	1 month
8	15.3	Female	VUR nephropathy	5 years	10 years	9 years
9	16	Female	Neural tube defect	At birth	8 years	-
10	16.6	Male	VUR nephropathy	6 years	?	-

CRF: Chronic renal failure; VUR: Vesicoureteric reflux

Table 2. Basal and post-treatment (4th and 6th month) parameters

	Pre-Treatment (Mean ± SD)	Post-Treatment (4th month) (Mean ± SD)	p	Post-Treatment (6th Month) (Mean ± SD)	p
Calcium(Ca)	9.03 ± 0.96 mg/dl	9.02 ± 1.03 mg/dl	0.981	9.30 ± 1.31 mg/dl	0.678
Phosphorus(P)	5.90 ± 1.34 mg/dl	5.02 ± 2.27 mg/dl	0.198	6.21 ± 1.87 mg/dl	0.943
Alkalen phosphatase (ALP)	1299.2 ± 1074.8 U/L	895.0 ± 946.5 U/L	0.014	505.1 ± 628.05 U/L	0.056
CaxP	53.59 ± 14.59	44.18 ± 17.46	0.070	51.48 ± 26.53	0.641
Intact PTH	519.18 ± 303.4 pg/ml	295.63 ± 398.3 pg/ml	0.027	151.73 ± 177.45 pg/ml	0.016
Osteocalcin	25.15 ± 3.76ng/ml	18.03 ± 5.69ng/ml	0.002	-	-
Calcitriol	17.12 ± 2.88 ng/ml	26.09 ± 8.64ng/ml	0.007	-	-
Growth rate	0.92 ± 1.59 cm/year	4.12 ± 4.85 cm/year	0.210	-	-
Creatinine clearance	19.72 ± 9.02 ml/min	14.93 ± 6.79 ml/min	0.062	-	-

serum PTH levels) (Table 2). Although basal and post-treatment serum osteocalcin and calcitriol levels were in the normal range, increment in serum calcitriol levels and decrement in serum osteocalcin levels were statistically significant ($p<0.05$) (Table 2). There was a significant correlation between pre-treatment and post-treatment serum osteocalcin-calcitriol levels multiplication ($p<0.01$) (Table 3). Also a significant correlation was observed in Δ osteocalcin-Δ calcitriol (basal and post-treatment levels difference) and %Δ osteocalcin-%Δ calcitriol relationship .

The changes of serum calcium (Ca), phosphorus (P), CaxP levels were not found statistically significant during the study protocol, serum alkaline phosphatase (ALP) levels declined significantly ($p<0.05$). During the study, 6 of 10 patients had no hypercalcemic episode. The incidence of hypercalcemia, hypocalcemia, hypophosphatemia, hyperphosphatemia were 15%, 17.5%, 20% and 15%, respectively. CaxP levels higher than 55 were accepted as a risk factor for visceral and soft tissue calcification. In seven patients CaxP levels were under this risk level in the first 4 months. In six month measurements CaxP level of the patients 4 and 7 were greater than 55, but there was no radiologic evidence of calcification though they were itching. Oral $CaCO_3$ dosages were not changed in patients 2, 3, 6, 8, 9, 10; twice in patient 7 and three times in patient 4. Oral calcitriol dosage was declined to 0.5 μg only in patient 6 because of over suppressing of serum PTH levels.

Parathyroid adenoma was observed only in patient 2 and when parathyroid US has been repeated at the end of the study, it disappeared.

There were 4 patients at the end of the 4th month whose serum iPTH levels were above 2.5 times of the normal levels. The pre-treatment serum iPTH levels of these patients (patients 2, 7, 8, 10) were significantly higher than those in the others (1178.25 ± 884 vs. 367.81 ± 203.8 pg/ml; $p<0.05$), and these patients had severe skeletal deformity and/or history of bone fracture. Chronic renal failure duration, therapy duration, and vitamin D dosage before the study were not significantly different in the groups with suppressed and high PTH.

Table 3. Correlation between the parameters which differed significantly with oral pulse calcitriol therapy

Correlation (Δ)	r	p
PTH-Osteocalcin	-0.2491	0.392
PTH-Calcitriol	0.3543	0.616
PTH-GFR	-0.4905	0.860
PTH-ALP	0.9004	0.005
Osteocalcin-Calcitriol	0.9108	0.008
Osteocalcin-GFR	0.2681	0.454
Osteocalcin-ALP	-0.3049	0.437
Calcitriol-GFR	0.0452	0.632
Calcitriol-ALP	0.3493	0.664
GFR-ALP	-0.4475	0.325

DISCUSSION

Calcitriol has been being used for 25 years for the treatment and protection of HPT and it has been shown that pulse calcitriol therapy can manage ROD succesfully (2, 3, 7, 11, 12, 17). IV pulse calcitriol therapy could produce higher serum vitamin D levels and inhibit PTH secretion without risks of the elevation of serum calcium levels, because the half life of the vitamin in the body was not long enough to increase the intestinal calcium absorption (intestinal by-pass). Intestinal by-pass can not be managed by intermittent oral pulse therapy, that's why theoratically risk of hypercalcaemia must be higher than that in IV therapy, but oral intermittent administration could prevent the risk of hypercalcaemia too, because of the shorter half life in the body. Although IV calcitriol treatment may have a superior effect on bone remodeling by influencing the levels of bone-resorptive cytokines as compared to the oral therapy, nowadays it is accepted that intermittent therapy is much mo-

re important than the route of the therapy (4, 18, 19).

In our study, we have considered that oral intermittent therapy could produce sufficient serum calcitriol levels which suppress serum iPTH levels. We used intermittent oral high dose 1,25 (OH)2 vitamin D3 in 10 patients with refractory secondary HPT. Serum iPTH levels decreased in all patients (mean %53.5) at the end of the 4th month. PTH suppression was observed in the first month in six patients, but in the remaining four patients (non-responders), PTH supression could not be achieved at the end of the 4th month. There was a significant inverse correlation between PTH supression and basal serum PTH levels ($p<0.05$). Non-responders had severe skeletal deformity and/or walking disability. In patients with lower basal serum PTH levels, slight skeletal deformities or no skeletal deformities, short therapy periods (1-2 month) could suppress PTH levels. It is known that long time PTH suppression at low levels could result in osteomalasia, that's why daily high dose calcitriol therapy must be stopped when there is a risk of hypercalcemia and intermittent therapy should be carried on. On the other hand, the duration of therapy of non-responders should be kept longer. Quarles et al. (13) reported that IV and oral pulse calcitriol therapies are not effective in patients who are on HD for a long time with severe secondary HPT and don't change the risk of parathyroidectomy. In our study, patient 8 was resembling the patients whom Quarles defined. This patient had used IV pulse therapy for 4 months before our protocol, but she remained as a non-responder. In the same patient, serum PTH levels decreased gradually and in the 6th month of the therapy serum AP levels became normal. Based on the observation of this patient, non-responders' therapy duration must be evaluated before regarding the therapy as ineffective.

Serum calcitriol levels were in physiologic ranges before and after oral pulse therapy in all patients, but post-treatment levels were significantly higher than pre-treatment levels. Quarles et al. (12) found physiologic serum calcitriol levels with oral pulse calcitriol therapy like us and showed that there are no additional advantages of pharmacological serum calcitriol levels which Slatopolsky (14) had suggested. They also showed maximal PTH mRNA inhibition with physiologic calcitriol concentrations in vitro. Our results support these findings.

Osteocalcin is a bone protein which is stimulated by calcitriol; however, in our study, serum osteocalcin levels decreased as a result of oral pulse calcitriol therapy. Also Malberti (8) reported similar results with IV calcitriol therapy. It is known that high PTH levels accompany high osteocalcin levels; therefore decrement in serum osteocalcin must be dependent on the decrement of PTH levels at the same time. On the other hand, Martinez (9) found higher serum osteocalcin levels with calcitriol therapy and he thought that it is due to stimulatory effect of calcitriol. In our study, when serum osteocalcin levels had been decreasing, serum calcitriol levels had been increasing simultaneously. There must be a significant relationship between osteocalcin and calcitriol levels like Ca-P relationship and multiplication of these two parameters could be on an equilibrium in the body.

Hypercalcemia is the most important complication of the calcitriol treatment. In our study, hypercalcemia occurred in 15% of all measurements and 6 of 10 patients had no hypercalcemic episode. Cano et al. (2) reported hypercalcemic episode in 11% when they used oral pulse calcitriol therapy twice a week. This risk ratio is close to ours, but we think that it is better to attempt oral pulse calcitriol therapy twice a week if there is high risk of hypercalcemia.

In our study, parathyroid glands could be imaged only in one patient with parathyroid US. She was a non-responder in the 4th month, but in the 6th month US, her parathyroid glands (adenoma?) disappeared. Fukogawa et al (6) reported that secondary HPT was easily controlled in patients without any detectable gland and remained or relapsed in patients with detectable glands. But we couldn't show parathyroid glands in 3 non-responder patients in any period of the therapy; that's why we think that parathyroid US is not a reliable method to determine the efficacy and prognosis of the pulse calcitriol therapy.

According to our results, bone pain was the most frequent symptom of secondary HPT and in patients without bone pain, secondary HPT could be suppressed easily. If bone pain persists despite calcitriol therapy, it could be accepted as an evidence of refractory secondary HPT. Walking disability was the second frequent symptom of our patients and it was observed in patients with higher basal and post-treatment PTH levels. Walking disability drammatically disappeared also in non-responders at the end of the 1st month of the therapy.

In conclusion, our results indicate that oral pulse calcitriol therapy is well tolerated and this treatment can suppress PTH levels without increasing hypercalcemia risk in patients with refractory secondary HPT.

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