Effects of Dietary Phosphorus Restriction on Secondary Hyperparathyroidism in Hemodialysis Patients during Intermittent Oral High-dose 1,25(OH)₂D₃ Treatment

Tsutomu TABATA, Shigeichi SHOJI, Atsuko MORITA, Masanori EMOTO,
Takashi INOUE, Takami MIKI¹, Yoshiki NISHIZAWA¹,
and Hirotooshi MORII¹

Division of Medicine, Inoue Hospital, Suita 564, Japan

¹*Second Department of Internal Medicine, Osaka City Medical School,
1-5-7, Asahi-machi, Abeno-ku, Osaka 545, Japan*

Summary Phosphorus (P) retention plays an important role in the pathogenesis of secondary hyperparathyroidism (2nd HPT) in chronic renal failure. In recent years, periodic intravenous or intermittent oral administration of high doses of 1,25(OH)₂D₃ has been reported to improve severe 2nd HPT in hemodialysis patients. The present study was performed to determine the effects of dietary P restriction on 2nd HPT in hemodialysis patients treated with intermittent oral high-dose 1,25(OH)₂D₃. A high dose of 1,25(OH)₂D₃ was administered orally twice a week at the end of hemodialysis in 20 hemodialysis patients with 2nd HPT. Dietary P content was estimated from records of the patients' food intake, made twice during the treatment period. Based on this information, dietitians developed appropriate meal plans and instructed the patients. After 8 weeks of the treatment, serum c-parathyroid hormone (c-PTH) and alkaline phosphatase (ALP) levels decreased significantly, from 18.8 ± 1.9 ng/ml and 347.1 ± 30.7 U/liter to 9.4 ± 1.2 ng/ml and 268.3 ± 19.6 U/liter, respectively. Serum P levels increased gradually during the first 4 weeks of the treatment. Dietary P intake was reduced significantly, from 908 ± 49 mg/day to 734 ± 39 mg/day, after the nutritional instructions. As a result of the dietary P restrictions, serum P levels were significantly decreased in the 8th week as compared with those in the 4th week. Serum Ca levels remained unchanged throughout the observation period. There was a significant relationship between the mean values for serum P levels during the study and the percent suppression of serum c-PTH. These results suggest that dietary P restriction facilitates serum P control without increasing doses of phosphate binders, and that this ameliorates 2nd HPT during intermittent oral high-dose 1,25(OH)₂D₃ treatment in hemodialysis patients with this condition.

Key Words phosphorus restriction, 1,25(OH)₂D₃, hemodialysis, hyperparathyroidism

Many hemodialysis patients suffer from uremic bone diseases, i.e., secondary hyperparathyroidism (2nd HPT) and osteomalacia, which occur either alone or in combination. Although oral administration of $1,25(\text{OH})_2\text{D}_3$ or $1\text{-}\alpha(\text{OH})\text{D}_3$ has been used to treat renal osteodystrophy, the treatment of 2nd HPT still remains as one of the most important problems in hemodialysis patients. Vitamin D metabolites may induce hypercalcemia and uncontrollable hyperphosphatemia in hemodialysis patients with severe 2nd HPT (1,2), and as a result, surgical parathyroidectomy might become necessary for these patients. Since Slatopolsky *et al.* first reported that periodic intravenous administration of $1,25(\text{OH})_2\text{D}_3$ was effective in lowering parathyroid hormone (PTH) levels without elevation of serum calcium (Ca) levels in severe 2nd HPT, numerous investigation have shown improvements of 2nd HPT in hemodialysis patients with this treatment (3). It was suggested that high levels of $1,25(\text{OH})_2\text{D}_3$ could directly suppress PTH production through the suppression of mRNA transcription of PTH synthesis in the parathyroid glands (4–6). It has recently been reported that intermittent oral high-dose $1,25(\text{OH})_2\text{D}_3$ treatment effectively lowered serum PTH levels in hemodialysis patients with refractory 2nd HPT (7,8).

Phosphorus (P) retention plays an important role in the pathogenesis of 2nd HPT in chronic renal failure (9,10). Hyperphosphatemia is associated with a decrease in the activity of the renal enzyme, 1-hydroxylase, which is responsible for the conversion of $25(\text{OH})\text{D}_3$ to $1,25(\text{OH})_2\text{D}_3$ (11). In patients with moderate renal insufficiency, restriction of dietary P increases the production of $1,25(\text{OH})_2\text{D}_3$, with concomitant decreases of serum PTH levels (12,13). However, this effect of dietary P restriction may not be operative in hemodialysis patients with highly advanced renal insufficiency, since the decrease in renal mass may severely limit the production of $1,25(\text{OH})_2\text{D}_3$. Recently, Lopez-Hilker *et al.* showed that reduction in dietary P in advanced renal insufficiency improved 2nd HPT through a mechanism that was independent of $1,25(\text{OH})_2\text{D}_3$ or plasma ionized Ca levels (14).

The present study was designed to determine whether dietary P restriction could lower serum PTH levels effectively in hemodialysis patients with 2nd HPT during intermittent oral high-dose $1,25(\text{OH})_2\text{D}_3$ treatment.

SUBJECTS AND METHODS

Twenty hemodialysis patients with 2nd HPT were the subjects of the study. Their ages ranged from 28 to 62 years (45.3 ± 2.1 years, mean $\pm$ SE) and in average the duration of hemodialysis was 97.2 ± 10.0 months. All patients had chronic glomerulonephritis. These patients were dialyzed three times a week with bicarbonate dialysate containing 3.0 mEq/liter of calcium. The serum c-PTH levels before the study ranged from 8.0 ng/ml to 44.0 ng/ml (mean 18.8 ± 1.9 ng/ml). The daily doses of $1\text{-}\alpha(\text{OH})\text{D}_3$ (Alfarol[®], Chugai Pharmaceutical Co., Tokyo, Japan) received before this study were 0.5 to 1.75 $\mu\text{g/day}$.

Three micrograms of $1,25(\text{OH})_2\text{D}_3$ (Rocaltrol[®], Nippon Roche, Tokyo, Japan) was administered orally twice a week at the end of hemodialysis for the first 4 weeks followed

by 4.0 μ g of the vitamin, administered in the same way, for the second 4 weeks. Throughout the treatment period, the patients took the same doses of calcium carbonate or aluminum hydroxide, as phosphate binders, as they had taken before this study.

Serum P, Ca, and alkaline phosphatase (ALP) levels were measured before, and in the 2nd, 4th, 6th, and 8th week of the treatment. Serum c-PTH levels were measured before and in the 4th and 8th week of the treatment.

Dietitians estimated the energy, protein, phosphorus, and calcium which had been consumed daily, using the detailed records of the patients' usual food intake, twice during this study, before the treatment and during the second 4 weeks of the treatment. Dietitians developed an appropriate meal plan and instructed the individual patients to reduce dietary P intake to under 1000 mg/day, based on the information obtained.

The results are expressed as means $\pm$ SE. Statistical analysis was performed with Student's *t* test.

RESULTS

Figure 1 shows the changes in serum c-PTH and ALP levels during the intermittent oral high-dose 1,25(OH)₂D₃ treatment. Serum c-PTH levels decreased significantly in the 4th week of the treatment; in the 8th week of the treatment, these levels reached 9.4 ± 1.2 ng/ml, which was 49.9% of the initial level. Serum alkaline phosphatase levels decreased significantly, from 347.1 ± 30.7 U/liter to 287.5 ± 23.3 U/liter, in the 8th week of the treatment.

The changes in serum levels of P and Ca during the study are shown in Fig. 2. Serum P levels increased gradually during the first 4 weeks of the treatment, and those in the 4th week were significantly higher than the initial levels (6.5 ± 0.3 mg/dl vs. 5.8 ± 0.2 mg/dl). After patients received the dietary instructions on P intake from the dietitians, serum P levels decreased significantly, to 5.6 ± 0.3 mg/dl in the 8th week as compared with those in the 4th week. Serum Ca levels remained unchanged throughout the observation period.

Figure 3 shows the daily intake of energy, protein, Ca, and P before and after the dietary instructions were received. Although daily phosphorus intake decreased significantly, from 908 ± 49 mg/day to 734 ± 39 mg/day, after the instructions, daily intake of energy, protein, and calcium also decreased significantly.

Figure 4 shows the relationship between the mean serum P levels during the treatment and the percentage of serum c-PTH levels suppressed by the treatment. There was a significant relationship between the mean serum P levels and the percentage of serum c-PTH suppressed.

DISCUSSION

We observed an effect similar to that of the intravenous administration of 1,25(OH)₂D₃ through the intermittent oral high-dose vitamin D administration used in this treatment of 2nd HPT in hemodialysis patients. This result is in agreement with those of previous studies (7,8).

Fig. 1. Effects of intermittent oral high-dose 1,25(OH)₂D₃ administration on serum c-PTH and ALP levels in 20 hemodialysis patients with 2nd HPT. Points represent the mean $\pm$ SE.

* $p < 0.05$, ** $p < 0.001$: significantly different from initial values.

Serum P levels increased gradually during the first 4 weeks of the treatment, before dietary P restriction. The elevation of serum P levels might result from increases in P absorption produced by the high dose of 1,25(OH)₂D₃ (15). Some investigators have reported that to prevent hypercalcemia during intermittent oral administration of high-dose 1,25(OH)₂D₃, they used aluminum hydroxide, but not calcium carbonate, as an oral phosphate binder (7,8). However, there is a possible danger of aluminum (Al) toxicity, especially Al-related osteomalacia, with the use of large doses of Al-containing gels in some patients as their serum PTH levels decrease. The development of Al-related osteomalacia has been reported to be one of the postoperative complications of total or subtotal parathyroidectomy (16,17). If calcium carbonate were to be used as a phosphate binder during the high-dose vitamin D treatment, hemodialysis with a dialysate containing a lower Ca concentration might be necessary to prevent hypercalcemia. Dietary P intake in excess of 1000 to 1200 mg/day may lead to hyperphosphatemia in hemodialysis patients,

Fig. 2. Effects of dietary phosphorus restriction on serum P and Ca levels during intermittent oral high-dose 1,25(OH)₂D₃ administration in 20 hemodialysis patients with 2nd HPT. Points represent the mean $\pm$ SE. The arrow indicates the time of nutritional instruction.

despite the intake of substantial amounts of phosphate binders. Dietary P restriction to under 1000 mg/day could facilitate the control of serum P with phosphate binders (18). We observed that daily P intake was reduced significantly, from 908 ± 49 mg/day to 734 ± 39 mg/day, after the patients received the nutritional instructions. This dietary P restriction significantly decreased serum P levels.

The intracellular P content of renal cortical cells is a major control mechanism for 1-alpha-hydroxylation of 25(OH)D (11). Hyperphosphatemia decreases the activity of the renal enzyme, 1 alpha hydroxylase. Several investigators have demonstrated that dietary P restriction increased plasma concentrations of 1,25(OH)₂D₃ in healthy subjects (19,20). In patients with moderate renal insufficiency, dietary P restriction increased 1,25(OH)₂D₃, with a concomitant normalization of plasma PTH levels (12,13). It was concluded that the normalization of plasma PTH by dietary P restriction was due to an increase in

Fig. 3. Daily intake of calories, protein, phosphorus, and calcium before and after nutritional instruction. Bars represent mean $\pm$ SE.

Fig. 4. Relationship between mean values of serum P levels during the treatment and percentage of serum c-PTH levels suppressed by the treatment in hemodialysis patients with 2nd HPT.

1,25(OH) $_2$ D $_3$ levels, since the plasma concentration of PTH varied inversely with that of 1,25(OH) $_2$ D $_3$. However, this mechanism may not be operative in hemodialysis patients, since the extreme decrease of renal mass may limit the production of 1,25(OH) $_2$ D $_3$.

Recently, Lopez-Hilker *et al.* reported that dietary P reduction in advanced renal insufficiency decreased serum PTH levels by a mechanism that was independent of the levels of 1,25(OH)₂D₃ (14). Although the mechanism underlying this effect is not well understood, they speculated that, potentially, P may affect the phospholipid composition of the parathyroid cell membrane, Ca fluxes in the parathyroid cells, and/or the regulation of 1,25(OH)₂D₃ receptors in the parathyroid cell. In the present study, we found a significant relationship between the percentage of serum c-PTH levels suppressed by the treatment and the mean values of serum P levels during the treatment. This suggests that phosphorus control may increase the suppressive effect of intermittent oral administration of 1,25(OH)₂D₃ in hemodialysis patients with 2nd HPT. Phosphorus retention may decrease the number of 1,25(OH)₂D₃ receptors in the parathyroid cell, which may reduce the ability of 1,25(OH)₂D₃ to directly inhibit PTH secretion. High levels of 1,25(OH)₂D₃ in the blood have been reported to directly suppress PTH secretion through the decreased production of mRNA for preproPTH in the parathyroid cell (4–6).

In conclusion, dietary P restriction facilitates serum P control and effectively ameliorates 2nd HPT during intermittent oral high-dose 1,25(OH)₂D₃ treatment.

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