Oral 1,25(OH)₂D₃ Pulse Therapy

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1,25(OH)₂D₃, renal osteodystrophy, secondary hyperparathyroidism, hemodialysis

Background of the development of "Oral 1,25(OH)₂D₃ Pulse Therapy."

In 1989, the authors first described the experience of oral 1,25(OH)₂D₃ pulse therapy as a pharmacological parathyroidectomy (1). This novel therapy for severe secondary hyperparathyroidism was developed by the authors against the following historical background. Many hemodialysis patients still suffer from secondary hyperparathyroidism even though active vitamin D metabolites, such as 1,25(OH)₂D₃ or 1α(OH)D₃, have been used to treat renal osteodystrophy for the last two decades. The failure in treating secondary hyperparathyroidism can be attributed to several factors. It is clear that many patients develop the disease simply because of poor patient compliance; they do not take phosphate binders and active vitamin D metabolites. However, it is also true that some patients develop the disease despite their good compliance. The main factor for treatment failure in the second group may be attributed to an insufficient dose of active vitamin D metabolite. In these patients, hypercalcemia frequently restricted the administration of 1,25(OH)₂D₃ or increments of the dose to a sufficient amount. In our dialysis centers, approximately 250 dialysis patients have been prescribed phosphate binders with 1,25(OH)₂D₃ or 1α(OH)D₃ for at least 5 years.

Of these patients, 38 suffered from osteitis fibrosa, with serum PTH levels, measured using a highly-sensitive PTH kit (HS-PTH: Yamasa Inc., Tokyo, Japan), higher than 10000 pg/ml. A number of studies, including some double-blind trials (2-4), had reported the clinical usefulness and limitations of 1,25(OH)₂D₃ by the beginning of the 1980s. Memmos et al. (2) reported that the dose of 1,25(OH)₂D₃ had to be reduced from 0.5 to 0.25 μg/day in 16 out of 27 patients during their 1-year double-blind trials, when serum calcium levels rose above 12 mg/dl in those patients. In many dialysis centers, hypercalcemia is a commonly encountered problem during treatment with 1,25(OH)₂D₃ or 1α(OH)D₃. Massry et al. (5) summarized these studies from the 1970s and concluded that hypercalcemia occurred with a dosage of 0.5-3.0 μg/day of 1,25(OH)₂D₃, but was more frequent with dosages of 1.0-2.0 μg/day. Brickman et al. (6) reported that as low a dosage as 0.14 μg/day, given for 2 weeks, induced severe hypercalcemia in 1 patient with osteitis fibrosa.

Hypercalcemia induced by 1,25(OH)₂D₃ usually occurs more frequently when secondary hyperparathyroidism develops to a severe stage, which is sometimes manifested in hyperplasia of the parathyroid glands. At this stage, pharmacological treatment usually failed to reverse the high PTH levels and surgical parathyroidectomy was the indicated treatment. However, parathyroidectomy causes a number of problems, such as recurrence of hyperparathyroidism from the residue of glands or autografted glands and osteomalacia due to levels of PTH which are too low.

In 1984, Slatopolsky et al. demonstrated the ability of intravenous 1,25(OH)₂D₃ to suppress secondary hyperparathyroidism (7). This report sug-
gested that a transient rise in serum 1,25(OH)2D3 level to the pharmacological level could suppress very high PTH levels without causing hypercalcemia. In 1989, the authors first demonstrated that oral administration of 4 μg 1,25(OH)2D3 twice a week could produce an effect similar to that of intravenous calcitriol; we referred to this therapy as "Oral 1,25(OH)2D3 Pulse Therapy" (pulse therapy) (1). Initial effects of pulse therapy.

We started this therapy with 9 hemodialyzed patients with serum c-PTH levels above 7.0 ng/ml (normal range in our facility: 0.20-1.00 ng/ml). We first administered 2 μg of 1,25(OH)2D3 orally twice a week at the end of hemodialysis and gradually increased the dosage to 6 μg each. As a result, we found that dosages of between 4 and 6 μg were sufficient to suppress the serum PTH level and that 4 μg caused less hypercalcemia (1).

After this "dose finding study," we tested the effectiveness of "Pulse therapy" with a dose of 4 μg in 19 hemodialyzed patients whose serum c-PTH levels were above 7.0 ng/ml (18.4±2.6 ng/ml) (8). Figure 1 shows the first 6-month course of the therapy. Both serum c-PTH and alkaline phosphatase (ALP) levels started to decrease significantly during the first month of therapy and reached their lowest levels by the end of the 5th month. Anova revealed that increments of serum calcium occurred during the 1st, 5th, and 6th months of the therapy. During the first 3 months, the pulse therapy was successful in all patients, without causing hypercalcemia. Three patients suffered from hypercalcemia during the 4th month of the study; these patients were withdrawn from the study. In this study, aluminum hydroxide was used as a phosphate binder and the calcium concentration of the dialysate was 3.5 mEq/l.

Effects of pulse therapy on X-ray findings.

Figure 2 shows the clinical course of the pulse therapy in a hemodialyzed 56-year-old female who showed the highest initial PTH level in our dialysis center (c-PTH: 48 ng/ml) (9). The intact PTH level (Allegro®) decreased to one-third

Figure 1  Sequential changes in serum levels of iPTH (HS-PTH) (●●●●), alkaline phosphatase (○○○○), calcium (●) and phosphorus (○) during the 6 months of oral pulse therapy (9). *p<0.05, **p<0.01 vs the previous value.

Figure 2  Clinical course of the pulse therapy in the most severe case (9).