Effects of 25(OH)-Vitamin D_3 in Hypocalcemic Patients on Chronic Hemodialysis

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The failure of 1,25,(OH)2-vitamin D_3 administration to result in complete healing of renal osteodystrophy in children has prompted trials with other preparations, such as 24,25,(OH)2-vitamin D_3.[1] Studies in animals and humans suggest that 24,25,(OH)2-vitamin D_3 decreases PTH secretion, stimulates bone mineralization, and promotes intestinal calcium absorption.[1] Improved bone mineralization was found in patients with severe osteomalacic lesions during combined treatment with 1,25,(OH)2-vitamin D_3 and 24,25,(OH)2-vitamin D_3.[2,3] Bordier *et al.*[4] reported that the effects of 25(OH)-vitamin D_3 on bone could be mimicked only by a combination of 1,25,(OH)2-vitamin D_3 and 24,25,(OH)2-vitamin D_3, suggesting that these metabolites may have a complementary action on bone mineralization. In addition, Hodsman *et al.*[2] found that administration of a combination of 1,25,(OH)2-vitamin D_3 and 24,25,(OH)2-vitamin D_3 to osteodystrophic chronic renal failure patients led to an improvement in bone mineralization, an effect not achieved with the administration of 1,25,(OH)2-vitamin D_3 alone.

25(OH)-vitamin D_3 is the precursor to the two active hormones 1,25,(OH)2-vitamin D_3 and 24,25,(OH)2-vitamin D_3. Beneficial effects of 25(OH)-vitamin D_3 administration were demonstrated by Langman *et al.*[5] in juvenile osteodystrophy. Toxicity studies with 25(OH)-vitamin D_3 showed no acceleration in the deterioration of renal function in nondialyzed pediatric patients with chronic renal failure.[6]

Although there is evidence for the benefits of 24,25,(OH)2-vitamin D_3 administration, controversy remains. Dunstan *et al.*[7] found no benefit in the administration of 24,25,(OH)2-vitamin D_3 except in minimizing the hypercalcemic effect of 1,25,(OH)2-vitamin D_3 alone.

It is thus likely that 25(OH)-vitamin D_3 has several potential advantages over 1,25,(OH)2-vitamin D_3 given alone. First, it is metabolized to 1,25,(OH)2-vitamin D_3 and 24,25,(OH)2-vitamin D_3, both of which seem to be required in renal osteodystrophy, whereas 1,25,(OH)2-vitamin D_3 is not metabolized to 24,25,(OH)2-vitamin D_3. Second, 25(OH)-vitamin D_3 has a longer half-life than 1,25,(OH)2-vitamin D_3, which allows every other day or three times per week dosage, which may be desirable for hemodialysis patients. We undertook this study to evaluate the effectiveness of 25(OH)-vitamin D_3 in the treatment of hypocalcemia in patients on renal dialysis.

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Materials and Methods

Stable maintenance hemodialysis patients with hypocalcemia (Total serum Ca < 8.5 mg/dl; normal, 8.5 to 10.5) were included. Patients with a serum phosphorus level >5.5 mg/dl or receiving other vitamin D analogs were excluded.

Serum calcium was measured weekly to assess response and detect hypercalcemia. Phosphorus, parathyroid hormone (PTH), alkaline phosphatase, blood urea nitrogen (BUN), creatinine, and electrolyte levels were determined before starting treatment and every month during the study. PTH N-terminal was measured by the Nichols Institute (San Juan Capistrano, CA).

Protocol

Patients were started on 25(OH)-vitamin D_3 (Calderol, Organon, West Orange, NJ) at the recommended loading dose of 100 μg/day for 2 weeks, then changed to 100 μg every other day. The dose of the drug was subsequently adjusted according to the results of the weekly serum calcium, and treatment was continued for 10 weeks. The results were analyzed for statistical significance using the paired *t* test.

Results

The results are summarized in **Table 1.** Seven patients completed the study. All achieved normocalcemia, and the only episode of hypercalcemia (11.2 mg/dl) resolved within 1 week of stopping therapy. The average maintenance dose of 25(OH)-vitamin D_3 was 100 μg qod. For the patients as a group, serum phosphorus rose slightly but not significantly, and no significant changes in PTH or alkaline phosphatase were detected during the study period.

Discussion

Dosage Relationship to Hypercalcemia

Published results on the use of 25(OH)-vitamin D_3 are summarized in **Table 2.** Teitelbaum *et al.*[8] found that ad-

Table 1. Results

	Before	After	
Serum calcium	8.17 ± 0 17	9.63 ± 0.34	$P < 0.005$
Serum phosphorus	4.77 ± 0.37	5.48 ± 0.35	NS
PTH (8 to 24 ng/l)	63	66	NS
Alkaline phosphatase (57 to 154 IU/l)	230	222	NS

N = 7.
NS—not significant.

ministration of 100 μg/day of 25(OH)-vitamin D_3 orally caused hypercalcemia, which was corrected by reducing the dose to 40 mcg/day. On this therapy, noticeable improvement in bone lesions occurred, and serum inorganic phosphate levels remained essentially unchanged. According to Coen *et al.*,[9] administration of 25(OH)-vitamin D_3 in a dose of 0.5 to 0.75 μg/kg/day resulted in a favorable effect on renal osteodystrophy, compared with that obtained with 1,25,(OH)2-vitamin D_3 alone. Whitmer *et al.*[10] reported a long-term study done of three groups of children. One group was treated with 25(OH)-vitamin D_3 (50 μg/day), one was treated with 25(OH)-vitamin D_3 and additional oral calcium supplementation (0.5 to 0.75 g/day), and one received oral calcium supplementation alone (0.5 to 0.75 g/day). In those treated with a calcium supplement alone, aggravation of bone lesions during intermittent hemodialysis was observed. In those given 25(OH)-vitamin D_3 in a dosage of 50 μg/day, mineralization improved and marrow fibrosis disappeared. Some patients who received small doses of 25(OH)-vitamin D_3 (25 to 40 μg/day) showed no changes on roentgenograms, although histologic improvement was evident, whereas those who were given higher doses of 25(OH)-vitamin D_3 (100 μg/day) often had overt toxic effects, mainly hypercalcemia. Finally, patients who received 25(OH)-vitamin D_3 in addition to calcium supplementation had to have their treatment interrupted one or more times because their plasma calcium concentration had risen as high as 11.0 to 11.5 mg/100 ml.

These studies[8-10] indicate that a dose of 50 μg/day is an adequate average maintenance dose (usually after 2 to 8 weeks of 100 μg/day). Our results are consistent with these reports. Although this dose may result in occasional hypercalcemia, the incidence of this complication is less than that reported previously with the larger doses.

Effects on Serum Phosphorus

The patients included in this study had stable and well-controlled serum phosphorus levels before the initiation of 25(OH)-vitamin D_3 treatment. During the study, serum phosphorus levels rose slightly, but not significantly. It is known, however, that 25(OH)-vitamin D_3 increases phosphorus absorption from the gut. Sebert *et al.*[11] found that treatment of osteodystrophy with a combination of 25(OH)-vitamin D_3 and 1-alpha-hydroxycholecalciferol was complicated by hypercalcemia and hyperphosphatemia, in spite of an increase in the prescribed dosage of aluminum hydroxide. There was also aggravation of osteitis fibrosa associated with increasing levels of plasma phosphate and PTH. Thus to keep serum phosphate levels within the normal range, dietary phosphorus intake may need to be restricted further and the dose of phosphate binders may have to be increased.

Renal and Extrarenal Production of 1,25 and 24,25(OH)2-D_3 in Chronic Renal Failure

24,25,(OH)2-Vitamin D_3 Production. There is substantial evidence that extrarenal sites of synthesis for both 24,25,(OH)2-vitamin D_3 and 1,25,(OH)2-vitamin D_3 exist.[12] Many tissues in addition to the kidneys display hydroxylase activity *in vitro*. Kano *et al.*[13] summarized recent studies on the subject indicating that the formation of 24,25,(OH)2-vitamin D_3 may occur in bone,[14] cartilage,[15] or the gut in anephric patients and that this metabolite causes enhancement of intestinal absorption of calcium[16] and suppression of PTH secretion.[17]

Table 2. Summary of Studies Using 25 (OH)-Vitamin D_3

Reference	Dosage	Calcemic Effect	Phosphate Level	PTH Level	Alkaline Phosphatase Level
Coen G., 1983	50 μg qd (0.5 to 0.75 μg/kg/day)* (1)	Returned to normal from 7 to 10 mg/dl	Increased	Decreased	Increased in 70% of patients
Halloran, B., 1984	300 μg qod loading dose, 150 μg maintenance	Increased from 8.8 ± 0.2 to 9 ± 0.1 mg/dl	Increased		
Teitelbaum, S. L., 1976	100 μg/day for 2 mos, then 40 μg/day	Increased from 5.8 to 11.5 mg/dl	Unchanged	Decreased	Returned to normal
Sebert, J. L., 1980	50 μg/day†	Increased from 7 mg/dl to 11 mg/dl	Increased	Increased	Increased
Coen, G., 1979	A—50 μg/day B—100 μg/day	No change Increased to normal level, Ca level reached 11 mg/dl	No change Increased	No change Variable	No change Fall toward normal
Witmer, G., 1976	25 to 50 μg/day‡§	Increased to normal from 6.2 to 11 mg/dl	Variable	Variable	

* Combined with 1,25(OH)2 D_3.
† Combined with 1-a HCC.
‡ The study was done in children.
§ Plus oral calcium supplementation.

Generation of 24,25,(OH)2-vitamin D_3 in the various sites is dependent on the 24-hydroxylase enzyme system. Renal 24-hydroxylase seems to be stimulated mainly by plasma levels of 1,25,(OH)2-vitamin D_3 or normal serum calcium levels but suppressed by raised levels of PTH or serum calcium. However, the extrarenal 24-hydroxylase depends on increased levels of 25(OH)-vitamin D_3 as a substrate and appears not to be regulated by 1,25,(OH)2-vitamin D_3. According to Shany *et al.*,[3] 1,25,(OH)2-vitamin D_3 acts to stimulate only the renal hydroxylase system and is without effect upon the extrarenal system.

Furthermore, it has been possible to measure 24,25,(OH)2-vitamin D_3 in the circulation of both untreated anephric patients and anephric patients treated with 25,(OH)-vitamin D_3.[12] Before administration of vitamin D_3, and while 25(OH)-vitamin D_3 concentrations were normal, 24,25,(OH)2-vitamin D_3 concentrations were detected at low levels in the circulation. When the concentration of 25(OH)-vitamin D_3 was raised to supernormal levels by ingestion of large amounts of vitamin D_3, the concentration of circulating 24,25,(OH)2-vitamin D_3 rose in all patients in a substrate-dependent manner, although the rise noted in the anephric patients was less than that noted in normal subjects. Horst *et al.*[18] showed that in anephric humans, 24,25,(OH)2-vitamin D_3 could be synthesized extrarenally in the presence of very high serum levels of 25(OH)-vitamin D_3. Haddad *et al.*[19] suggested that the production of 24,25,(OH)2-vitamin D_3 is a major route of metabolism in anephric patients, accounting for 12% of the available 25(OH)-vitamin D_3 pool. Experiments in animals have shown that although 24,25,(OH)2-vitamin D_3 may not be formed outside the kidney under normal conditions, it is produced extrarenally in significant amounts when a high concentration of 25(OH)-vitamin D_3 is present.

Halloran *et al.*[20] showed that administration of large oral doses of 25(OH)-vitamin D_3 to patients on hemodialysis, with native kidney tissue *in situ*, results in substrate-dependent increases in 24,25,(OH)2-vitamin D_3, 25,26,(OH)2-vitamin D_3, and 1,25,(OH)2-vitamin D_3 in the circulation. They suggested that this may be due to residual renal hydroxylase activity but could not exclude extrarenal synthesis of these metabolites. Finally, Zerwekh *et al.*[21] investigated whether patients with renal failure on dialysis with or without intact kidneys have the capacity to produce 24,25,(OH)2-vitamin D_3. They found that when supernormal serum 25(OH)-vitamin D_3 concentrations were achieved by exogenous 25(OH)-vitamin D_3, there was a significant increase in all patients with chronic renal failure and in anephric subjects. The mean increase in serum 24,25,(OH)2-vitamin D_3 concentration correlated positively with the mean increase in serum 25(OH)-vitamin D_3 concentration.

1,25,(OH)2-Vitamin D_3 Production. Zerwekh *et al.*[21] also observed 1,25,(OH)2-vitamin D_3 levels and found an increase in serum 1,25,(OH)2-vitamin D_3 in three chronic renal failure patients with intact kidneys treated with 25(OH)-vitamin D_3, whereas under normal conditions the serum concentration of 1,25,(OH)2-vitamin D_3 is tightly regulated and independent of the serum concentration of 25(OH)-vitamin D_3. Halloran *et al.*[20] found a rise in levels of 1,25,(OH)2-vitamin D_3 after administration of 25(OH)-vitamin D_3 and concluded that substrate availability may be an important determinant of 1,25,(OH)2-vitamin D_3 levels in end-stage renal disease. Dusso *et al.*[22] reported that after therapy with 25(OH)-vitamin D_3, serum levels of 1,25,(OH)2-vitamin D_3 increased and remained higher for more than 2 weeks after discontinuation of the therapy. The levels of 1,25,(OH)2-vitamin D_3 in uremic dogs could thus be modified by changes in the levels of 25(OH)-vitamin D_3, emphasizing that substrate delivery plays an important role in the production of 1,25,(OH)2-vitamin D_3.

These data are in contrast to the findings of Taylor *et al.*[23] and Taylor,[24] who found undetectable levels of 24,25,(OH)2-vitamin D_3 in anephric subjects treated with vitamin D_3 or 25(OH)-vitamin D_3. This discrepancy might be explained by the relatively short period of 25(OH)-vitamin D_3 administration in their study (4 days). Using a comparable dose of 25(OH)-vitamin D_3, Zerwekh *et al.*[21] observed that not all patients demonstrated increases in serum 24,25,(OH)2-vitamin D_3 at the end of 2 weeks of therapy; 4 weeks or longer of daily 25(OH)-vitamin D_3 administration was required for all patients to achieve increased serum 24,25,(OH)2-vitamin D_3 concentration. This observation may indicate that extrarenal 25(OH)D-24-hydroxylase may have a higher Km than that of the renal enzyme.

In light of these results, it is probable that although residual renal hydroxylase activity may be present, extrarenal sites for the synthesis of 24,25,(OH)2-vitamin D_3 and 1,25,(OH)2-vitamin D_3 exist and can be stimulated by high serum levels of 25(OH)-vitamin D_3.

Conclusions

This study demonstrates that 25(OH)-vitamin D_3, in an initial dose of 100 μg/day for 2 weeks followed by 100 μg qod, is effective in treating the hypocalcemia of patients on maintenance hemodialysis. There was one episode of mild hypercalcemia noted, and no significant rise in serum phosphorus in any patient studied. There is evidence in the literature[12,22] that 25(OH)-vitamin D_3 is converted into both 1,25,(OH)2-vitamin D_3 and 24,25,(OH)2-vitamin D_3 in patients on maintenance hemodialysis, indicating that there are potential advantages of using 25(OH)-vitamin D_3 over 1,25,(OH)2-vitamin D_3 alone in these patients. Longer-term studies are needed to evaluate these potential advantages.

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