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E Slatopolsky, … , H Harter, K J Martin

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Research Article

Current evidence suggests that administration of 1,25(OH)2D3 to patients with chronic renal insufficiency results in suppression of secondary hyperparathyroidism only if hypercalcemia occurs. However, since the parathyroid glands possess specific receptors for 1,25(OH)2D3 and a calcium binding protein, there is considerable interest in a possible direct effect of 1,25(OH)2D3 on parathyroid hormone (PTH) secretion independent of changes in serum calcium. Recent findings indicate substantial degradation of 1,25(OH)2D3 in the intestine, therefore, it is possible that while oral administration of the vitamin D metabolite increases intestinal calcium absorption, the delivery of 1,25(OH)2D3 to peripheral target organs may be limited. We therefore compared the effects of orally or intravenously administered 1,25(OH)2D3 on the plasma levels of 1,25(OH)2D3 and the effects of these two modes of treatment on PTH secretion. Whereas oral administration of 1,25(OH)2D3 in doses adequate to maintain serum calcium at the upper limits of normal did not alter PTH levels, a marked suppression (70.1 +/- 3.2%) of PTH levels was seen in all 20 patients given intravenous 1,25(OH)2D3. Temporal studies suggested a 20.1 +/- 5.2% decrease in PTH without a significant change in serum calcium with intravenous 1,25(OH)2D3. In five patients the serum calcium was increased by the oral administration of calcium carbonate, the decrement in serum i-PTH was only 25 +/- 6.65% when compared with 73.5 +/- 5.08% (P […]

Marked Suppression of Secondary Hyperparathyroidism by Intravenous Administration of 1,25-Dihydroxycholecalciferol in Uremic Patients

Eduardo Slatopolsky, Carol Weerts, James Thielan, Ronald Horst, Herschel Harter, and Kevin J. Martin
Renal Division, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110; National Animal Disease Center, U. S. Department of Agriculture, Ames, Iowa 50010

Abstract. Current evidence suggests that administration of $1,25(OH)_2D_3$ to patients with chronic renal insufficiency results in suppression of secondary hyperparathyroidism only if hypercalcemia occurs. However, since the parathyroid glands possess specific receptors for $1,25(OH)_2D_3$ and a calcium binding protein, there is considerable interest in a possible direct effect of $1,25(OH)_2D_3$ on parathyroid hormone (PTH) secretion independent of changes in serum calcium. Recent findings indicate substantial degradation of $1,25(OH)_2D_3$ in the intestine, therefore, it is possible that while oral administration of the vitamin D metabolite increases intestinal calcium absorption, the delivery of $1,25(OH)_2D_3$ to peripheral target organs may be limited. We therefore compared the effects of orally or intravenously administered $1,25(OH)_2D_3$ on the plasma levels of $1,25(OH)_2D_3$ and the effects of these two modes of treatment on PTH secretion. Whereas oral administration of $1,25(OH)_2D_3$ in doses adequate to maintain serum calcium at the upper limits of normal did not alter PTH levels, a marked suppression (70.1±3.2%) of PTH levels was seen in all 20 patients given intravenous $1,25(OH)_2D_3$. Temporal studies suggested a 20.1±5.2% decrease in PTH without a significant change in serum calcium with intravenous $1,25(OH)_2D_3$. In five patients the serum calcium was increased by the oral administration of calcium carbonate, the decrement in serum i-PTH was only 25±6.65% when compared with 73.5±5.08% ($P < 0.001$) obtained by the administration of intravenous $1,25(OH)_2D_3$. Thus, a similar serum calcium achieved by intravenous $1,25(OH)_2D_3$ rather than calcium carbonate has a greater suppressive effect in the release of PTH.

These studies indicate that $1,25(OH)_2D_3$ administered intravenously rather than orally may result in a greater delivery of the vitamin D metabolite to peripheral target tissues other than the intestine and allow a greater expression of biological effects of $1,25(OH)_2D_3$ in peripheral tissues. The use of intravenous $1,25(OH)_2D_3$ thus provides a simple and extremely effective way to suppress secondary hyperparathyroidism in dialysis patients.

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Introduction

Secondary hyperparathyroidism is a universal complication of chronic renal insufficiency (1, 2). Since parathyroid hormone (PTH)[1] acts upon the kidney to increase the production of $1,25(OH)_2D_3$ (3–5), which in turn increases intestinal calcium absorption, it seems possible that a negative feedback system could operate to regulate PTH secretion. In severe renal insufficiency the lack of $1,25(OH)_2D_3$ could thus be a factor in maintaining the hypersecretion of PTH. There is substantial evidence that treatment with $1,25(OH)_2D_3$ in chronic renal disease may result in severe hypercalcemia and consequent suppression of PTH secretion (6). However, if hypercalcemia does not occur, PTH levels do not change. Since the parathyroid glands possess specific receptors for $1,25(OH)_2D_3$ (7) and a calcium binding protein (8), there is considerable interest in whether $1,25(OH)_2D_3$ per se, independent of hypercalcemia,

1. *Abbreviation used in this paper:* PTH, parathyroid hormone.

may play a role in the regulation of PTH secretion. To date, this issue remains controversial (9–15).

Because recent studies have shown substantial degradation of $1,25(OH)_2D_3$ in the intestine (16), we reasoned that while oral administration of $1,25(OH)_2D_3$ may inrease intestinal calcium absorption, the degradation of the vitamin D metabolite may impair the delivery of $1,25(OH)_2D_3$ to other peripheral target organs and thus limit the expression of direct biological effects.

Accordingly, the present studies were designed to examine the effects of orally and intravenously administered $1,25(OH)_2D_3$ on the levels of $1,25(OH)_2D_3$ achieved in plasma and the effects of these therapies on PTH secretion.

Methods

20 hypocalcemic patients, 9 females and 11 males, who underwent dialysis 4 h per session, three times per week using a hollow fiber dialyzer were selected for study. Residual creatinine clearance was <1 ml/min in all patients. The age ranged from 21 to 67 yr. Nine patients had nephrosclerosis, six had diabetes mellitus, three had polycystic kidneys, one had medullary cystic disease and another, pyelonephritis. Written consent was obtained in all patients and the research protocol was approved by the Human Studies Committee of Washington University. The study was divided into three parts:

(*a*) Control. During the control period blood samples were obtained anaerobically, without stasis, before dialysis, three times per week for a period of 3 wk. (*b*) Treatment. After base-line data had been obtained, $1,25(OH)_2D_3$ (calcitriol) was given intravenously at the end of each dialysis, three times per week for a period of 8 wk. The initial dose was 0.5 μg and was gradually increased to a maximum of 4.0 μg per dialysis treatment. The maximum dose of $1,25(OH)_2D_3$ administered to each patient ranged from 1.75 to 4.0 μg. The final dose ranged from 0.5 to 4.0 μg. $1,25(OH)_2D_3$ was temporarily discontinued if the serum calcium was >11.5 mg/100 ml or if the calcium-phosphate product was greater than 70. (*c*) Posttreatment. After 8 wk of treatment, $1,25(OH)_2D_3$ was discontinued and blood was obtained before dialysis three times per week for a period of three weeks.

Long-term studies. $1,25(OH)_2D_3$ was restarted in two patients with severe secondary hyperparathyroidism at the end of the posttreatment period. The dose of $1,25(OH)_2D_3$ ranged between 1.0 and 1.5 μg, three times per week. The patients received the medication for a period of 1 yr.

Comparison of plasma levels of $1,25(OH)_2D_3$ after intravenous or oral administration. In two patients 2 μg of $1,25(OH)_2D_3$ was given i.v. and blood samples were obtained after 2, 15, 30, and 60 min and after 2, 4, 6, and 24 h. 1 wk later, similar studies were repeated, except that 2 μg of $1,25(OH)_2D_3$ was given orally (the 2- and 15-min samples were omitted).

The effects of the oral administration of $1,25(OH)_2D_3$. In three patients with secondary hyperparathyroidism of varying severities, $1,25(OH)_2D_3$ was given orally, 0.5 μg daily for a period of 6 mo. Serum calcium was maintained at the upper limits of normal.

The effects of oral administration of calcium carbonate. In five patients at the end of the studies, when the serum calcium returned to hypocalcemic levels (8.4±0.4 mg/100 ml), calcium carbonate (Os-Cal 500) was given for a period of 3 mo (dose, 3–6 g/d) to achieve the same serum calcium levels observed during the administration of intravenous $1,25(OH)_2D_3$ (peak calcium 10.9 mg/100 ml).

Analytical methods. Total and ionized calcium, phosphorus, magnesium, and radioimmunoassayable PTH (i-PTH) were determined in all blood samples. A complete blood count and SMA-18 were obtained at the beginning and end of each section of the study. Total serum calcium and magnesium were measured by atmoic absorption spectrometry (Perkin-Elmer Corp., Instrument Div., Norwalk, CT, model 503). Serum ionized calcium was measured by an ion specific flow-through electrode (Orion Research Inc., Cambridge, MA, model SS20). Serum phosphorus was measured by Auto-Analyzer II. Immunoreactive PTH was measured with antiserum CH9. This antiserum has been fully characterized in our laboratory (17) and recognizes the intact hormone, the mid-region and the carboxy-terminal portion of the PTH molecule. In current terminology, this antiserum should be considered as a mid-region/C-terminal antiserum. In order to increase the precision of the radioimmunoassay for PTH, all 42 samples per patient were measured in quadruplicate or sextuplicate in the same assay. Plasma levels of $1,25(OH)_2D_3$ were measured as previously described (18).

Results

Short-term studies of intravenous calcitriol administration. Fig. 1 illustrates the effect of $1,25(OH)_2D_3$ on total serum calcium in a representative patient. The dashed bars indicate the amount of $1,25(OH)_2D_3$ given per dialysis. The moderate hypocalcemia observed during the control period was reversed during $1,25(OH)_2D_3$ administration. Serum calcium levels increased to 10.9 mg/100 ml and subsequently decreased to subnormal values in the posttreatment period. The changes in total serum calcium for all 20 patients are illustrated in Fig. 2. The *n* value represents the total number of observations. The mean plasma calcium level during the control period was 8.5±0.3 mg/100 ml. During intravenous administration of $1,25(OH)_2D_3$, the mean serum calcium increased to 9.4±0.3 mg/100 ml with a peak response of 10.9±0.3 mg/100 ml. In the posttreatment period, serum calcium decreased to a mean

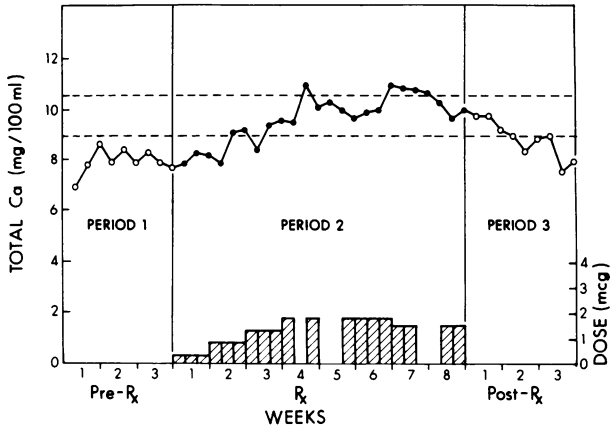

Figure 1. The effect of intravenous $1,25(OH)_2D_3$ (calcitriol) on total serum calcium in a representative patient. The dashed bars indicate the amount of $1,25(OH)_2D_3$ given per dialysis. If the serum calcium was >11.5 mg/100 ml or the $CaPO_4$ product >70, $1,25(OH)_2D_3$ was omitted.

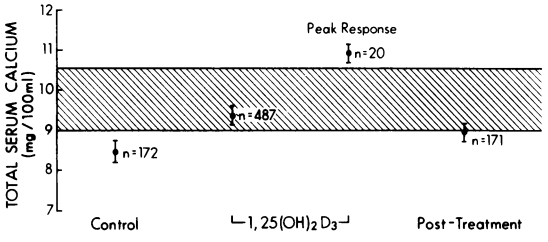

Figure 2. Values of total serum calcium before, during, and after the administration of intravenous $1,25(OH)_2D_3$ to all 20 patients. Values are shown as mean±SE. The peak response is the mean of the highest serum calcium achieved in each patient during $1,25(OH)_2D_3$ treatment.

of 9.0±0.3 mg/100 ml. Similar changes were observed in ionized calcium. During the control period mean I_{Ca} was 4.1±0.1 mg/100 ml, it increased to 4.8±0.1 mg/100 ml (peak response 5.4±0.1 mg/100 ml) during $1,25(OH)_2D_3$ treatment, and decreased to 4.2±0.1 mg/100 ml after $1,25(OH)_2D_3$ was discontinued.

In general, serum phosphorus tended to increase during $1,25(OH)_2D_3$ administration. Thus, the amount of phosphate-binders administered to the patients was adjusted to maintain the levels of serum phosphorus relatively constant. Serum magnesium did not change during the entire study in all 20 patients.

The percent changes in the values for serum i-PTH are illustrated in Fig. 3. In all patients there was a substantial decrease in the levels of i-PTH during intravenous $1,25(OH)_2D_3$ treatment with a mean decrement of 70.1±3.2% ($P < 0.001$). After $1,25(OH)_2D_3$ was discontinued i-PTH increased in all patients. Fig. 4 demonstrates the sequential effect of intravenous $1,25(OH)_2D_3$ on serum i-PTH levels in seven patients with

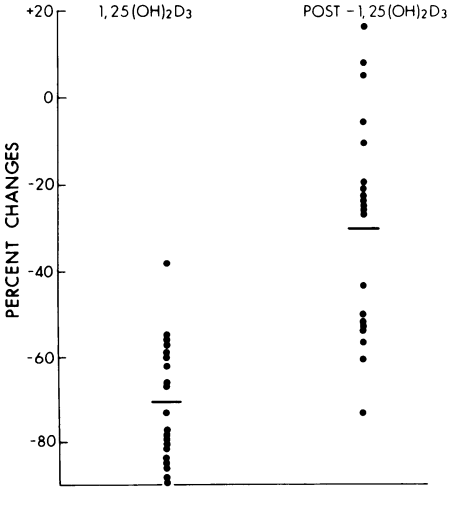

Figure 3. Changes in serum i-PTH during and after the administration of intravenous $1,25(OH)_2D_3$ expressed as percent of pre-treatment i-PTH values. The mean decrement in serum i-PTH was 70%.

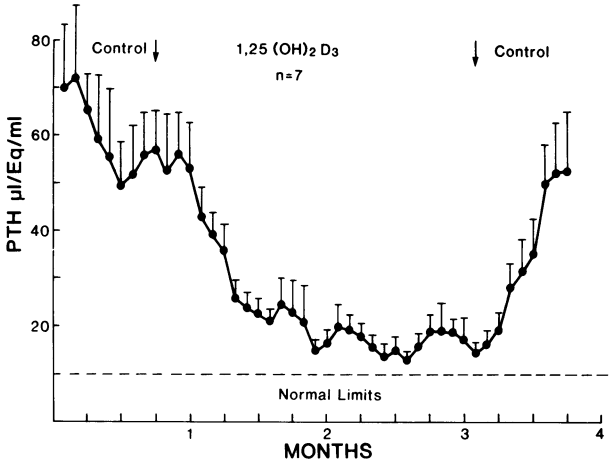

Figure 4. Sequential changes in serum i-PTH in patients with mild hyperparathyroidism before, during and after treatment with $1,25(OH)_2D_3$. An 86% decrease in the levels of i-PTH was observed during intravenous $1,25(OH)_2D_3$ administration.

mild secondary hyperparathyroidism. An 86% decrease in the levels of i-PTH was observed. After $1,25(OH)_2D_3$ was discontinued, i-PTH rose to pretreatment levels. The temporal relationship between ionized calcium and serum i-PTH, in a group of six patients with moderate secondary hyperparathyroidism, is depicted in Fig. 5. During the first 3 wk of treatment with $1,25(OH)_2D_3$, ionized calcium did not change from base line, however serum i-PTH decreased from a mean of 132±20 to 95±25 µleq/ml. There was a subsequent gradual increase in ionized calcium from 4.1±0.14 mg/100 ml to 5.3±0.2 mg/

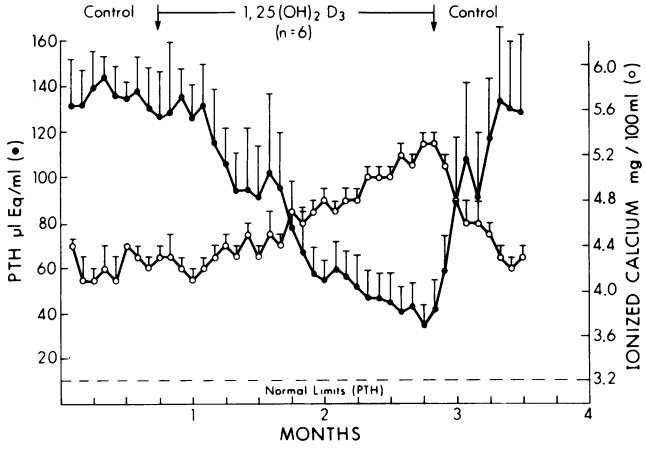

Figure 5. Temporal relationship between ionized calcium and serum i-PTH, before, during and after intravenous $1,25(OH)_2D_3$ administration in patients with moderate hyperparathyroidism. The maximum decrement in i-PTH was 73.5%. In the first 3 wk of treatment with $1,25(OH)_2D_3$ there was no change in ionized calcium, however, serum i-PTH decreased from 132±20 to 95±20 µleq/ml.

100 ml and i-PTH decreased further to 35±9 μleq/ml. Thus the overall fall in i-PTH was 73.5%. Again, after $1,25(OH)_2D_3$ was discontinued i-PTH rose to pretreatment levels.

Fig. 6 illustrates the relationship between serum i-PTH (closed bars) and ionized calcium (open bars) in all 20 patients during $1,25(OH)_2D_3$ treatment. In the first 10 d of the treatment period, there was an insignificant increase in the levels of ionized calcium (<0.1 mg/100 ml), however, i-PTH decreased by 20% ($P < 0.001$). To further examine a potential direct effect of $1,25(OH)_2D_3$ in addition to the effect of calcium on serum levels of i-PTH we compared the increments in ionized calcium and the percent decrease in serum i-PTH from control values. Three hundred-twenty-nine observations were evaluated. For simplicity, only mean values are depicted (Fig. 7). There was a significant correlation ($P < 0.001$) between the increase in ionized calcium and the decrease in i-PTH, illustrating the crucial role of calcium in the suppression of PTH. However, at 0 increment in ionized calcium the regression line intercepted the ordinate at 80% of the original value, suggesting that in addition to the marked suppressive effect of calcium on PTH, $1,25(OH)_2D_3$, per se, also affected the release of PTH in uremic patients.

Long-term studies of intravenous calcitriol administration. To determine if the suppression of i-PTH induced by the intravenous administration of $1,25(OH)_2D_3$ was a temporary event, long-term studies were performed. Two patients with severe secondary hyperparathyroidism were selected for this study. Fig. 8 illustrates the results in one of the patients. During the control period i-PTH averaged 316±9.1 μleq/ml. After administration of $1,25(OH)_2D_3$ the values decreased to 101 μleq/ml. Subsequently after $1,25(OH)_2D_3$ was discontinued

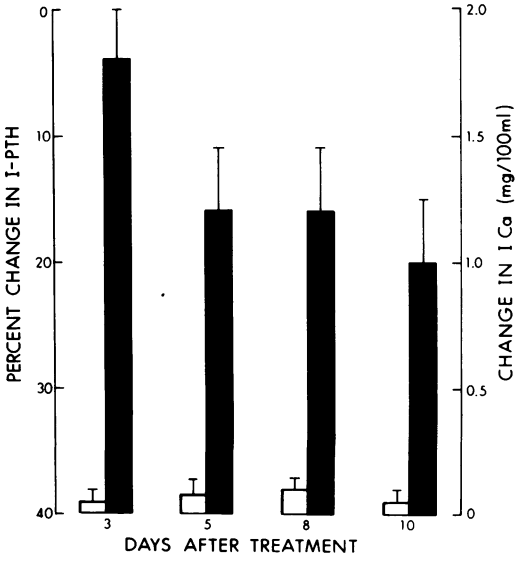

Figure 6. Relationship between serum i-PTH (closed bars) and ionized calcium (open bars) in all 20 patients during the first 10 d of treatment with intravenous $1,25(OH)_2D_3$.

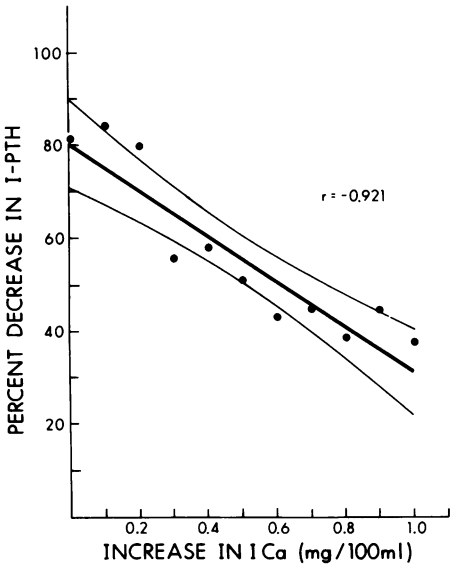

Figure 7. Relationship between the decrement in i-PTH and increment in ionized calcium for all patients during the entire two months of treatment with intravenous $1,25(OH)_2D_3$ (for complete description, see text).

iPTH increased to 298 μleq/ml and after 1 yr of intravenous $1,25(OH)_2D_3$ treatment i-PTH decreased to 25 μleq/ml for an overall decrease of 92.1% of the pretreatment levels of iPTH. Similar results were obtained in the second patient (i-PTH decreased from 1036 μleq/ml to 78 μleq/ml). The dose of $1,25(OH)_2D_3$ was decreased to 1.0 to 1.5 μg three times per week. With this dose the serum calcium was maintained between 10.3 and 10.9 mg/100 ml.

Comparison of oral and intravenous administration of calcitriol. To determine the changes in serum $1,25(OH)_2D_3$, studies were performed after the administration of $1,25(OH)_2D_3$ given intravenous or orally. Fig. 9 describes the results obtained in one patient after the administration of 2.0 μg of $1,25(OH)_2D_3$. The levels of serum $1,25(OH)_2D_3$ seen during the peak response

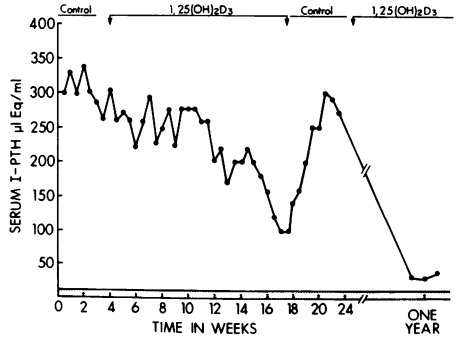

Figure 8. Long-term effects of intravenous $1,25(OH)_2D_3$ on i-PTH in a representative patient. After 1 yr of treatment the decrement in serum i-PTH was 92.1% control.

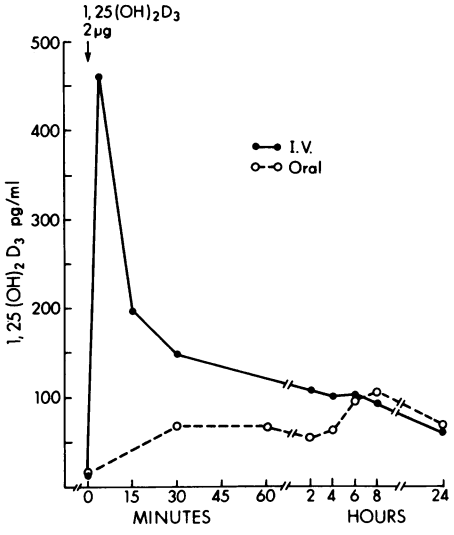

Figure 9. Serum levels of $1,25(OH)_2D_3$ in a representative patient after the administration of 2.0 μg of $1,25(OH)_2D_3$ given intravenously (● —— ●) or orally (o - - - o).

with the intravenous preparation were approximately fourfold higher in comparison with the values obtained after the oral administration. Similar results were obtained in the second patient. The peak value was 720 pg/ml after the intravenous dose vs. 189 pg/ml after the oral dose.

Long-term studies of oral calcitriol administration. Fig. 10 describes the results obtained in three patients during the oral administration of $1,25(OH)_2D_3$, at a dose of 0.5 μg daily for a period of 6 mo. Despite the fact that serum calcium was in

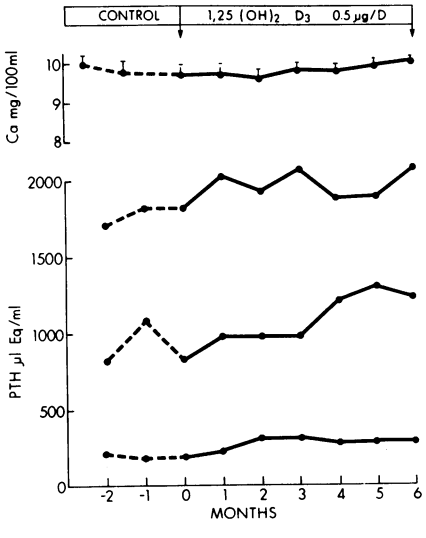

Figure 10. Long-term effects of $1,25(OH)_2D_3$ given orally (0.5 μg/d) on serum calcium and serum i-PTH in three patients maintained on chronic hemodialysis.

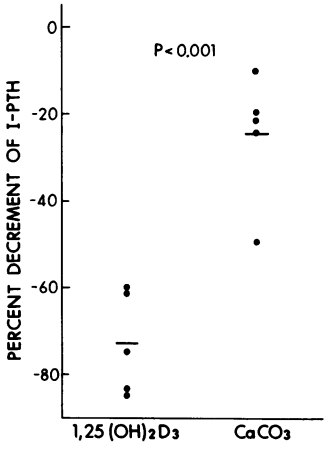

Figure 11. The effects of intravenous $1,25(OH)_2D_3$ or calcium carbonate on i-PTH in five patients. A 73.5±5.08% decrease in the levels of i-PTH was observed during intravenous $1,25(OH)_2D_3$ administration. The administration of calcium carbonate decreased the levels of i-PTH by only 25±6.65% ($P < 0.001$).

the upper limits of normal, there was no apparent effect on the levels of circulating i-PTH.

The effects of oral administration of calcium carbonate. Fig. 11 describes the results obtained in five patients during the intravenous administration of $1,25(OH)_2D_3$ or after the administration of calcium carbonate. Despite similar increments in serum calcium, the degree of parathyroid hormone suppression was greater (73.2±5.08%) during the administration of intravenous $1,25(OH)_2D_3$ than that observed after calcium carbonate (25±6.65%), $P < 0.001$. The initial level of i-PTH was the same (125±19 vs. 131±22 μleq/ml) before intravenous $1,25(OH)_2D_3$ or calcium carbonate administration, respectively. The increment in serum calcium was the same (peak 10.9±0.3) with both medications.

Discussion

High levels of radioimmunoassayable parathyroid hormone are present in patients with primary and secondary hyperparathyroidism. In primary hyperparathyroidism ~90% of the patients have an adenoma of the parathyroid glands, and hypercalcemia is usually seen in this disorder. On the other hand, patients with secondary hyperparathyroidism have hyperplasia of all four parathyroid glands and hypocalcemia. Although in these two conditions there is a greater amount of parathyroid tissue and, therefore, secretion of PTH is greatly increased, it appears that, in addition to an increase in prathyroid tissue, other mechanisms may also be involved in the abnormal secretion of PTH observed in these patients (19, 20). The concentration of serum ionized calcium is the primary factor that controls the secretion of PTH. In the past decade a variety of agents in addition to calcium have been shown to modify the secretion of parathyroid hormone (21). Several investigators (9–11) have provided evidence that vitamin D metabolites directly affect regulation of PTH secretion. In 1974 Oldham et al. (8) isolated a calcium-binding protein from porcine parathyroid glands with properties similar to those of the calcium-binding proteins found in mammalian

intestinal mucosa. The administration of $25(OH)D_3$ to rachitic puppies increased the calcium binding protein in the parathyroid glands. Subsequently, Brumbaugh et al. (7) demonstrated specific binding of $1,25(OH)_2D_3$ to cytosolic and nuclear receptors of the chick parathyroid glands in vitro. In the same year Henry and Norman (22) gave [^{3}H]$1,25(OH)_2D_3$ to vitamin D-deficient chicks and extracted the lipid content of several tissues. They found that the radioactive material was incorporated into intestine and parathyroid glands at four times the blood level. Chertow et al. (9) subsequently performed studies in vivo in the rat and in vitro with bovine parathyroid gland slices. These investigators clearly demonstrated an inhibitory effect of $1,25(OH)_2D_3$ on PTH release. However, after these initial publications a series of papers appeared in the literature, suggesting that $1,25(OH)_2D_3$ did not have a direct effect on the secretion of parathyroid hormone (13, 14). Because of these controversial results, we studied in great detail the effect of $1,25(OH)_2D_3$ on parathyroid hormone secretion in vitro, using bovine parathyroid gland slices and isolated dispersed bovine parathyroid cells (15). Because of the heterogeneity of the circulating fragments of parathyroid hormone we used two radioimmunoassays to measure PTH in the culture medium. A midregion/carboxy-terminal and a specific amino-terminal antisera were used in our studies. In addition, extensive analysis of the multiple forms of i-PTH by polyacrylamide gel electrophoresis also was determined. The results from the dual radioimmunoassay as well as the characterization by polyacrylamide gel electrophoresis failed to demonstrate an effect of $1,25(OH)_2D_3$ on PTH secretion by the isolated bovine parathyroid cells or by bovine parathyroid slices. It is critical to emphasize that the parathyroid glands used in these studies were obtained from normal cows which were not depleted of $1,25(OH)_2D_3$. Moreover, the studies were performed in vitro and the incubations were conducted over a 4-h period. The fact that the animals were not depleted of $1,25(OH)_2D_3$ may have had an effect on the outcome of the results obtained in these studies. Studies by Oldham and collaboratores (23) in vitamin D-deficient dogs clearly indicated that higher concentrations of calcium were necessary to suppress the release of parathyroid hormone in these animals. When similar studies were performed in the same animals, after $1,25(OH)_2D_3$ was given to the dogs, the parathyroid glands appeared to be more sensitive to mild increments in serum calcium.

It is known that parathyroid glands obtained from uremic patients have a shift in the set point for calcium suppression of PTH release (19, 20). A higher concentration of ionized calcium than normal is required to suppress PTH release in secondary hyperparathyroidism. The set point for calcium is defined as the amount of calcium necessary to suppress 50% the release of PTH. Brown and collaborators (19, 20) working with normal dispersed human parathyroid cells found a set point for PTH release at a calcium concentration of 0.97 ± 0.04 mM, but in patients with secondary hyperparathyroidism the set point was increased to 1.26 ± 0.3 mM. The degree of suppression of hormone secretion with an increasing calcium concentration is apparently less from cells obtained from hyperplastic glands than normal glands. Several factors can thus lead to elevated serum parathyroid levels in uremic patients. These include: (*a*) an increase in tissue mass caused by the cell hypertrophy/hyperplasia; (*b*) an increase in the set point for calcium to inhibit hormone secretion; and (*c*) a change in the degree of suppression by calcium throughout the calcium sensitive range (i.e., slope of the suppression line). Because calcium is an inhibitor of the adenylate cyclase activity in isolated parathyroid cell membranes, and the adenylate cyclase enzyme plays a role in the regulation of parathyroid hormone secretion, further studies were performed in our laboratory (24) to characterize the activity of this enzyme in membranes obtained from patients with hyperparathyroidism. These studies demonstrate that the hyperparathyroid gland enzyme was less susceptible to inhibition by calcium requiring 0.7 to 1.0 mM calcium for 50% inhibition of adenylate cyclase, whereas comparable inhibition of the normal adenylate cyclase was seen at 0.22 to 0.28 mM ionized calcium. It is possible, therefore, that this abnormality in the regulation of the adenylate cyclase may also prticipate in the abnormal secretion of PTH in addition to the enlarged mass of tissue.

The low levels of $1,25(OH)_2D_3$ observed in patients with advanced renal insufficiency (25–28) may potentially play a role in the abnormal behavior of the parathyroid glands. Madsen and collaborators (29) studied the effects of intravenous $1,25(OH)_2D_3$, 250 ng every 6 h, in ten patients with acute oliguric renal failure. In these patients serum ionized calcium was maintained constant and at a subnormal level by continuous peritoneal dialysis. A significant suppression of PTH levels was observed in the patients receiving $1,25(OH)_2D_3$. The authors concluded that since the serum calcium was maintained constant by the dialysis procedure, $1,25(OH)_2D_3$ per se suppressed the release of parathyroid hormone. Similar positive results were obtained by Berl and collarobators (6) in 16 patients with chronic renal insuffiiency. The patients received up to 1.5 μg/d of $1,25(OH)_2D_3$ for a period of 12 wk. Parathyroid hormone decreased from 1,077 to 595 μleq/ml. After the $1,25(OH)_2D_3$ was discontinued, i-PTH increased to 1165 μleq/ml. In this study, however, since there was a remarkable increase in the levels of serum calcium and very early samples were not obtained, it is difficult to know if the suppression of PTH was due to an elevation of ionized calcium per se or if there was an additional direct effect of $1,25(OH)_2D_3$.

In our studies all patients had a marked suppression in the levels of i-PTH. In some of the patients the levels of i-PTH approximated the normal range obtained in our laboratory. Other investigators (30), including ourselves, using $1,25(OH)_2D_3$ orally have observed a lesser degree of suppression of secondary hyperparathyroidism if marked hypercalcemia did not occur (Fig. 10). In view of the difference in the levels of $1,25(OH)_2D_3$ in plasma obtained after intravenous or oral administration, it is possible that the changes induced in the secretion of the parathyroid glands may be different according to the mode of administration of $1,25(OH)_2D_3$. Moreover, since uremic pa-

tients seldom receive more than 1.0 μg of $1,25(OH)_2D_3$ per day by the oral route, the blood levels of $1,25(OH)_2D_3$ likely will be even lower than those obtained in our studies, where 2.0 μg of $1,25(OH)_2D_3$ was given orally. When $1,25(OH)_2D_3$ is given orally, intestinal calcium absorption is markedly increased. The $1,25(OH)_2D_3$ is metabolized in the intestine and the levels observed in plasma are only slightly elevated. Support for this concept was presented by Napoli and collaborators (16). These investigators demonstrated the existence of a new C-24 oxidation pathway for the metabolism of $1,25(OH)_2D_3$. Homogenates of intestinal mucosa converted $1,25(OH)_2[26,27\text{-}^3H]D_3$ into two new metabolites. Intravenous $1,25(OH)_2D_3$ may thus result in relatively increased delivery of this agent to other tissues including the parathyroid glands.

Rasmussen and collaborators (31) demonstrated that in addition to the classic theory on the mechanism of action of vitamin D, the so-called genome, $1,25(OH)_2D_3$ per se affects the lipid composition of intestinal brush border membrane, increasing the transcellular transport of calcium. Potentially, the high concentration of $1,25(OH)_2D_3$ in plasma seen after intravenous administration may thus induce a greater degree of suppressibility of the parathyroid glands. Of course, we have no proof that in our studies the high levels of $1,25(OH)_2D_3$ seen in the serum of our patients, after intravenous injection of $1,25(OH)_2D_3$, may have changed the cellular influx of calcium into the parathyroid gland. If this hypothesis is correct, possibly higher levels of serum calcium may be necessary to suppress secondary hyperparathyroidism when a patient receives oral $1,25(OH)_2D_3$ than when $1,25(OH)_2D_3$ is given intravenously.

In summary, the present studies demonstrate that 1,25-dihydroxy cholecalciferol given intravenously has a greater suppressive effect on the release of PTH than $1,25(OH)_2D_3$ given orally. The major effects on PTH release appeared to be due to an elevation in serum calcium. However, it would seem that in addition to the calcemic effect, $1,25(OH)_2D_3$ per se modifies the secretion of PTH. It is known that parathyroid glands obtained from uremic patients have a shift in the set point for calcium requiring a higher concentration of ionized calcium than normal parathyroid glands for the suppression of PTH release. These studies raise the possibility that $1,25(OH)_2D_3$ may affect the regulation of PTH, making the gland more sensitive to calcium. Obviously, further studies are necessary to clarify this point. Finally, the results obtained in these studies differ from our previous observations. However, we must emphasize that our original work was performed in vitro, using short-term incubations up to 4 h with $1,25(OH)_2D_3$ using glands obtained from normal animals that were not deficient in $1,25(OH)_2D_3$.

The implication of the present studies is that complete evaluation of the peripheral effects of oral $1,25(OH)_2D_3$ may be limited by the enhanced local effect upon intestinal calcium absorption, leading to hypercalcemia. The hyperabsorption of calcium limits the dose of $1,25(OH)_2D_3$ which can be administered. The quantity of $1,25(OH)_2D_3$ available to peripheral tissues may be further reduced by intestinal degradation of the vitamin D metabolite. Intravenous administration of $1,25(OH)_2D_3$, on the other hand, may allow greater delivery to peripheral tissues such as the parathyroid glands and allow for expression of biological effects at these sites. Regardless of the mechanism of action, the main implication of these studies is the impressive clinical utility of the intravenous $1,25(OH)_2D_3$ in dialysis patients. $1,25(OH)_2D_3$ can be easily given intravenously at the end of each dialysis. The patient's compliance is assured and for the first time this study showed a significant decrease in the levels of i-PTH in all 20 patients studied. A "medical parathyroidectomy" can now be easily accomplished.

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