# Parathyroid Hormone Suppression by Intravenous 1,25-Dihydroxyvitamin D

## A Role for Increased Sensitivity to Calcium

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## Abstract

**Numerous in vitro studies in experimental animals have demonstrated a direct suppressive effect of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) on parathyroid hormone (PTH) synthesis. We therefore sought to determine whether such an effect could be demonstrated in uremic patients undergoing maneuvers designed to avoid changes in serum calcium concentrations. In addition, the response of the parathyroid gland in patients undergoing hypercalcemic suppression (protocol I) and hypocalcemic stimulation (protocol II) before and after 2 wk of intravenous $1,25(OH)_2D$ was evaluated. In those enlisted in protocol I, PTH values fell from 375±66 to 294±50 pg ($P < 0.01$) after $1,25(OH)_2D$ administration. During hypercalcemic suppression, the "set point" (PTH max + PTH min/2) for PTH suppression by calcium fell from 5.24±0.14 to 5.06±0.15 mg/dl ($P < 0.05$) with $1,25(OH)_2D$. A similar decline in PTH levels after giving intravenous $1,25(OH)_2D$ was noted in protocol II patients. During hypocalcemic stimulation, the parathyroid response was attenuated by $1,25(OH)_2D$. We conclude that intravenous $1,25(OH)_2D$ directly suppresses PTH secretion in uremic patients. This suppression, in part, appears to be due to increased sensitivity of the gland to ambient calcium levels.**

## Introduction

Despite many advances in understanding the pathogenesis of secondary hyperparathyroidism in uremia, optimal treatment remains an elusive goal. In part, the difficulty in controlling parathyroid hormone (PTH) secretion relates to a relative insensitivity of the uremic gland to suppression by calcium. Several in vitro studies (1, 2) suggest that the concentrations of calcium necessary to decrease PTH secretion is higher in the hyperplastic than in normal glands. Thus, in uremia, adequate suppression of PTH secretion may require high, but potentially toxic serum calcium levels. Furthermore, it has been demonstrated that the parathyroid cells contain receptors for 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) (3, 4) and this metabolite decreases PTH secretion independent of ambient calcium levels (5–7). In part, this suppressant effect appears to result from decreased gene transcription of preproPTH mRNA (8–11). Because uremic patients usually demonstrate low serum levels of $1,25(OH)_2D$ (12–14), one could postulate that abnormalities in the vitamin D–PTH axis contribute to the development of secondary hyperparathyroidism. We evaluated this relationship by administering intravenous (IV)[1] $1,25(OH)_2D$ to 20 hemodialysis patients for a period of 8 wks (15). PTH levels decreased by 20% before a rise in serum calcium levels. Overall, we noted a 70% decline in PTH concentrations when calcium levels were maintained at the upper limits of normal. This suggested a direct suppressant effect of $1,25(OH)_2D$ on the secretion of the parathyroid glands. We could not, however, rule out imperceptible changes in serum calcium during the study nor was the mechanism for PTH suppression during IV $1,25(OH)_2D$ investigated.

Accordingly, the present studies were designed to examine the effects of IV $1,25(OH)_2D$ on PTH levels under conditions that were specifically manipulated to prevent an increase in serum calcium. In addition, we sought to determine the effects of $1,25(OH)_2D$ on the parathyroid gland responsiveness to hypercalcemic suppression and hypocalcemic stimulation.

## Methods

*Protocol I: hypercalcemic suppression.* 10 anuric patients maintained on chronic hemodialysis for > 2 yr (mean 4.7 yr) were selected for study. All patients manifested evidence of severe secondary hyperparathyroidism with amino-terminal biologically active PTH levels > 100 pg/ml (normal < 20 pg/ml). The causes of the renal failure were hypertension ($n = 6$), diabetes ($n = 2$), chronic glomerulonephritis ($n = 1$), and unknown ($n = 1$). No patient had received a vitamin D preparation within the 1 mo before study nor were any patients ingesting medications (anticonvulsants, steroids, etc.) that potentially interfered with mineral metabolism. All were undergoing dialysis of 3–4 h duration three times a week with a standard acetate dialysate containing 3.5 meq/liter of calcium. Oral calcium carbonate, used in a manner previously described (16), was prescribed to optimize long-term calcium and phosphorus levels. In those patients who developed hypercalcemia (Ca > 11 mg/dl) or who had uncontrollable hyperphosphatemia (phosphorus > 7 mg/dl), aluminum-containing phosphorus binders (ACPB) were added to the regimen. All patients were on a stable calcium carbonate and ACPB regimen for the 1 mo before the initiation of the study. The mean amount of elemental calcium ingested was 2,514±506 mg/d and aluminum 915±276 mg/d. The diet consisted of a 0.9 g/kg per d protein and 650–800 mg phosphorus per day. During a midweek standard dialysis the patients underwent a continuous calcium chloride infusion at a rate of 3 mg/kg per h of elemental calcium. Blood for PTH, ionized calcium (ICa), phosphorus, and magnesium was obtained at frequent intervals during the infusion. The first three subjects had blood sampled at 0, 15, 30, and 60 min and

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1. *Abbreviations used in this paper:* ACPB, aluminum-containing phosphorus binders; ICa, ionized calcium; IV, intravenous.

hourly thereafter. We found, however, that the major changes in PTH levels occurred very early during the infusion making analysis of the rapid PTH response to calcium uninterpretable. The remaining seven patients underwent an identical calcium infusion with blood obtained at 0, 5, 10, 20, 30, and 60 min and hourly thereafter for a total of 3 h. After the control calcium infusion, intravenous $1,25(OH)_2D$ (3 $\mu$g) was administered following each dialysis for 2 wk. In order to prevent increases in serum calcium levels during this period, the dialysate calcium was decreased to 2.5 meq/liter and oral calcium was discontinued. Predialysis calcium and phosphorus levels were measured with each treatment and ACPB were adjusted in an attempt to keep phosphorus levels constant. The amount of aluminum ingestion during the 2-wk interval was 1351±214 mg/d. No dietary changes were instituted. At the end of the 2-wk interval, a calcium infusion was repeated in a manner identical to that of the control.

In order to quantify the sensitivity of the parathyroid gland to calcium suppression we determined the "set point." This term was defined as that calcium concentration which caused a 50% decline in PTH levels (PTH max + PTH min/2) during each infusion.

*Protocol II: hypocalcemic stimulation.* The second set of experiments was designed to determine the effect of IV $1,25(OH)_2D$ on the PTH response to acute hypocalcemia induced by a low calcium dialysate. Eight patients were chosen with the same clinical characteristics and exclusion criteria as protocol I with the exception that four had severe hyperparathyroidism and four demonstrated mild hyperparathyroidism (PTH < 50 pg/ml). The etiologies of the renal failure were hypertension ($n$ = 5), diabetes ($n$ = 2), and chronic pyelonephritis ($n$ = 1). The amount of calcium and aluminum ingested before the protocol were 2,301±414 g/d and 658±253 mg/d, respectively. The oral aluminum load during the protocol was 1,112±161 mg/d.

The protocol was identical to that of protocol I except, instead of performing two calcium infusions, the patients underwent two dialysis treatments with a dialysate containing 1 meq/liter of calcium. During these hypocalcemic dialyses, ICa decreased by ~ 1.5 mg/dl. Blood for PTH, ionized calcium, phosphorus, and magnesium were determined at 0, 2, 5, 10, 20, 30, and 60 min and then hourly for a total of 3 h. In addition, blood was obtained for $1,25(OH)_2D$ levels before the study. Trough levels of $1,25(OH)_2D$ were also determined at least twice in each patient during the study period.

*Protocol III: aluminum studies.* In order to evaluate the effects of IV $1,25(OH)_2D$ on aluminum levels, 10 additional patients were selected to undergo the same maneuvers as in the first two protocols but without the induction of acute hypocalcemia or hypercalcemia. Predialysis aluminum levels were measured for 1 wk before the protocol. The amount of aluminum prescribed was then increased from 554±312 to 1,222±380 mg/d during the subsequent 2 wk while the patients received IV $1,25(OH)_2D$. Aluminum levels were drawn before each dialysis.

Written consent was obtained on all patients and the research protocol was approved by the Human Studies Committee of Washington University.

*Assays and materials.* Serum ionized calcium was measured by an ion-specific flow-through electrode (model 5520, Orion Research, Inc., Cambridge, MA). Serum phosphorus was determined by Auto-Analyzer II and magnesium by atomic absorption spectrometry (model 503, Perkin-Elmer Corp., Instrument Div., Norwalk, CT). The radioimmunoassay for PTH employed the antiserum CH9N which was developed in our laboratory. The characteristics of this amino-terminal assay have been described previously (17). Plasma levels of $1,25(OH)_2D$ were measured by the method of Reinhardt et al. (18). The characterization of the assay by our laboratory has been published elsewhere (19). All samples from each patient were determined in sextuplicate in the same assay. Aluminum levels were determined by flameless atomic absorption spectophotometry (20) (graphite furnace model HGA-400, Perkin-Elmer Corp.). The interassay coefficient of variation was 9.1% and intraassay coefficient of variation 8.5%.

IV $1,25(OH)_2D$ was generously supplied by Abbott Laboratories (North Chicago, IL).

*Statistics.* Statistical analysis utilized Student's $t$ test for parametric paired data or signed rank analysis for nonparametric PTH values. Results are presented as mean±SEM.

## Results

*Protocol I: hypercalcemic suppression.* The levels of ICa and PTH before and after 2 wk of IV $1,25(OH)_2D$ in 10 patients are shown in Fig. 1. The ICa concentrations fell from 4.89±0.19 to 4.68±0.17 mg/dl ($P$ = NS) after IV $1,25(OH)_2D$. Thus, the described maneuvers (2.5 meq/liter Ca dialysate and discontinuation of oral calcium carbonate) were successful in avoiding an increase of calcium during $1,25(OH)_2D$ therapy. Under these circumstances, there was a significant fall in PTH levels from 375±66 to 294±50 pg/ml ($P < 0.01$). There were no significant alterations in pre-dialysis phosphorus (6.37±0.49 vs. 6.73±0.37 mg/dl) and magnesium levels (2.33±0.08 vs. 2.30±0.10 mg/dl). Thus, despite no changes in ICa, the PTH levels fell by 22% with IV $1,25(OH)_2D$.

The effects of IV $1,25(OH)_2D$ on PTH secretion during a calcium infusion in a representative patient are shown in Fig. 2. The control predialysis PTH and ionized calcium levels were 333 pg/ml and 4.68 mg/dl, respectively. During the control infusion, PTH levels initially fell in concert with the rising ICa. However, after 30 min the PTH levels remained fairly constant despite progressive hypercalcemia. The set point (defined in Methods) was an ionized calcium of 5.04 mg/dl. After 2 wk of IV $1,25(OH)_2D$, the PTH level fell to 314 pg/ml despite a slight decline in ionized calcium to 4.62 mg/dl. In the early phase of the repeat calcium infusion, the PTH levels dropped dramatically in the face of lower calcium values compared to those of the control. During the latter part of the infusion the PTH concentrations were not different from control. Therefore, after the administration of IV $1,25(OH)_2D$, the patient had a shift in the set point from 5.04 to 4.64 mg/dl.

The changes in the set point in each patient before and after $1,25(OH)_2D$ are shown in Fig. 3. The baseline set point during the calcium infusion was 5.24±0.14 mg/dl. After 2 wk of treatment, the set point decreased significantly to 5.06±0.15 mg/dl ($P < 0.05$).

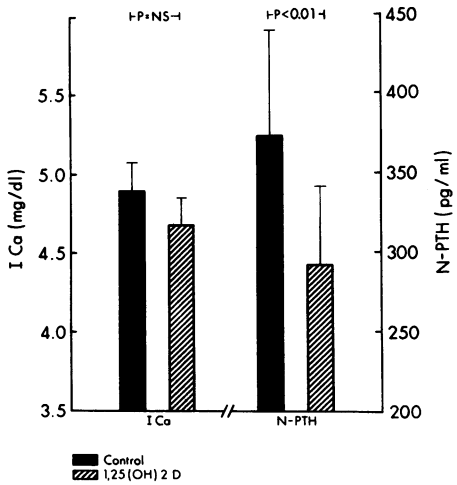


*Figure 1.* Serum levels of ICa and N-PTH in 10 patients before (*solid bars*) and after 2 wk of IV $1,25(OH)_2D$ (*hatched bars*). Despite no significant changes in ICa levels, the PTH values fell by 22% ($P < 0.01$) with IV $1,25(OH)_2D$.

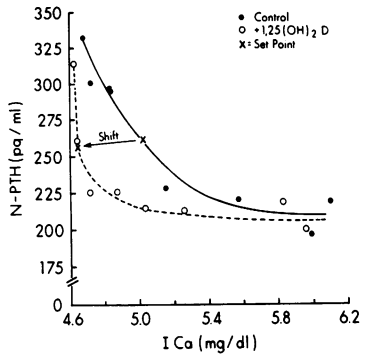


*Figure 2.* The effects of IV $1,25(OH)_2D$ on PTH secretion during a calcium infusion in a representative patient. During the control infusion (•) the set point (×) of ICa was 5.04 mg/dl. After 2 wk of IV $1,25(OH)_2D$, the PTH levels (○) fell despite a lower ICa value and the set point decreased to 4.64 mg/dl.

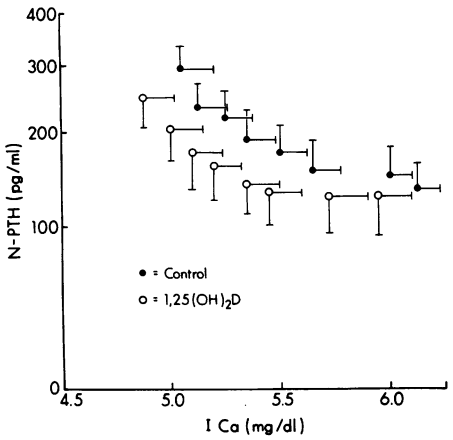


*Figure 4.* A composite graph of the PTH and ICa concentrations determined at each sampling time during the calcium infusions. Each point represents the PTH and ICa values±SEM determined at each sampling time during the infusion. (•) Results of the control calcium infusions; (○) values after IV $1,25(OH)_2D$.

A summary of the results of the calcium infusions is shown in Fig. 4. Early in the infusions, the PTH levels were lower in the presence of $1,25(OH)_2D$ than control despite comparable ICa levels. During the latter part of the infusion, when there was maximal suppression, the PTH values were not different.

*Protocol II: hypocalcemic stimulation.* Baseline PTH levels fell from 180±58 to 118±42 pg/ml ($P < 0.01$) after 2 wk of IV $1,25(OH)_2D$ (Fig. 5). There were no significant changes in ICa values (4.47±0.17 vs. 4.60±0.16 mg/dl). Phosphorus and magnesium levels were no different (5.40±0.76 vs. 5.94±0.36 and 2.48±0.12 vs. 2.67±0.10 mg/dl, respectively).

Following dialysis with low calcium dialysate, ICa and phosphorus levels fell by comparable amounts in both groups. The peak PTH concentration was 454±158 pg/ml during the control low calcium dialysis and 263±104 pg/ml ($P < 0.01$) during the low calcium dialysis after 2 wk of IV $1,25(OH)_2D$. These results are illustrated in Fig. 6. Thus, when the patients are analyzed as an aggregate, IV $1,25(OH)_2D$ appears to significantly impair the PTH response to hypocalcemic stimulation.

However, when the data was stratified according to the severity of the hyperparathyroid state a somewhat different picture emerged. In Fig. 7, the response of PTH to hypocalcemic stimulation is plotted against calcium values in those four patients with severe hyperparathyroidism (PTH > 100 pg/ml). During control studies, the PTH levels rose from a baseline of 327±38 pg/ml to a peak of 660±163 pg/ml. After treatment with $1,25(OH)_2D$, the baseline PTH concentrations fell to 218±42 pg/ml and reached a maximum stimulated value of 488±128 pg/ml. Thus, under both conditions, there was a twofold increase in maximally stimulated PTH values compared to baseline. The shape of the curves appeared to be similar. The curves of each individual patient are shown on Fig. 8.

The response of the gland to hypocalcemic stimulus in those patients with mild secondary hyperparathyroidism (PTH < 50 pg/ml) appeared to be qualitatively and quantitatively different. During the control dialysis, the baseline PTH levels rose threefold from 32±6 to 107±35 pg/ml (Fig. 9). After IV $1,25(OH)_2D$ the ICa values rose to the upper limits of normal in association with a fall in PTH to 18±3 pg/ml. During hypocalcemic stimulation, the rise in PTH was blunted. The peak PTH levels were 26±5 pg/ml, values less than twice baseline despite a mean ICa value of 3.5 mg/dl. Thus, patients with mild hyperparathyroidism show less sensitivity to the stimulatory effects of hypocalcemia with IV $1,25(OH)_2D$ compared to those with severe hyperparathyroidism. The curves of each individual patient are shown on Fig. 10.

Before the institution of IV $1,25(OH)_2D$, the serum levels of this metabolite were 15.4±2.5 pg/ml. Predialysis levels ob-

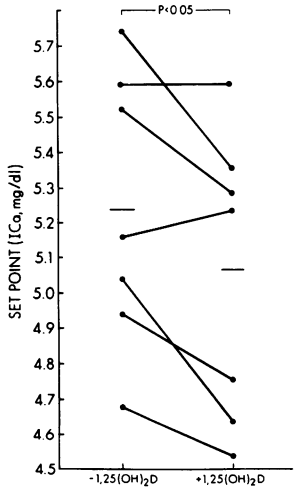


*Figure 3.* Changes in the set point in each patient before and after IV $1,25(OH)_2D$. After 2 wk of IV $1,25(OH)_2D$, the set point of ICa fell from 5.24±0.14 to 5.06±0.15 mg/dl, ($P < 0.05$ by rank sum analysis).

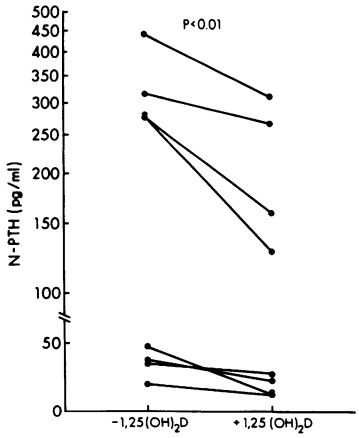


*Figure 5.* The PTH levels in eight patients undergoing protocol II. Despite no changes in ICa levels, the PTH concentrations fell significantly ($P < 0.01$).

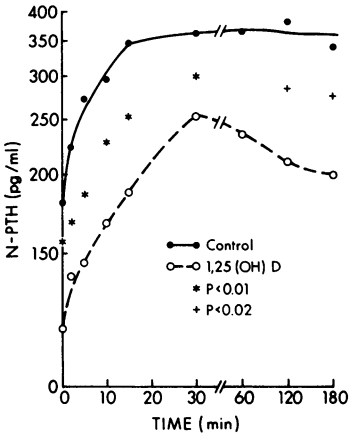


*Figure 6.* The PTH response to hypocalcemia before (●) and after (○) IV $1,25(OH)_2D$. At all sampling times except one, PTH levels were significantly lower after IV $1,25(OH)_2D$.

tained during the 2-wk protocol (40 h after the previous injection) were 46.1±3.9 pg/ml. The later values were slightly above our normal range of 20–35 pg/ml.

*Protocol III: aluminum studies.* The baseline aluminum levels were 41.8±3.2 μg/liter. During the 2-wk protocol, the mean aluminum levels were 41.2±3.1 μg/liter. The mean aluminum levels of the 10 patients after 2 wk of IV $1,25(OH)_2D$ were 38.7±5.1 μg/liter. Thus, it is unlikely that the maneuvers of protocols I and II influenced serum aluminum levels.

## Discussion

The results of these studies in human subjects lend additional support to the in vitro (5–10) and in vivo (11) data in experimental animals which have demonstrated a direct suppressant role for $1,25(OH)_2D$ on PTH synthesis. We cannot rule out a potential effect of $1,25(OH)_2D$ on another substance which, in turn, could suppress the parathyroid gland. However, no discernible changes in ICa, phosphorus or magnesium were noted. Our studies also complement an earlier report in humans by Madsen et al. (21). They studied the effects of IV $1,25(OH)_2D$, 250 ng every 6 h in 10 patients with oliguric

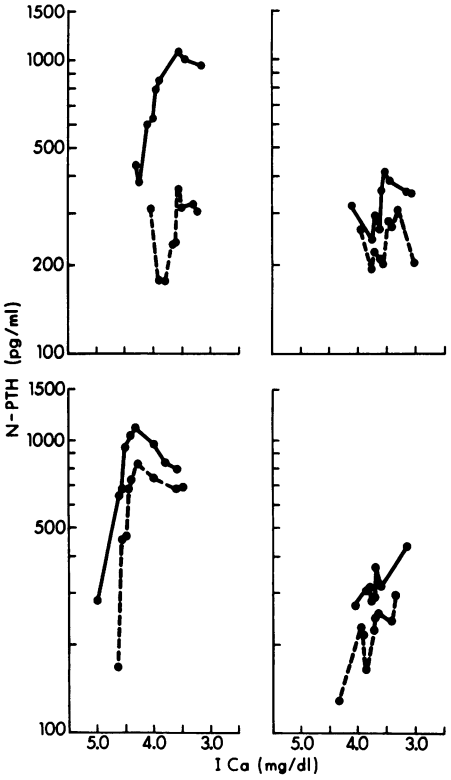


*Figure 8.* The response of PTH to hypocalcemic stimulation in each of the subjects with severe hyperparathyroidism. (——) Control; (- - -) 2-wk IV $1,25(OH)_2D$.

acute renal failure. Despite maintenance of constant and low levels of ICa with peritoneal dialysis, PTH levels fell significantly in those patients receiving $1,25(OH)_2D$. Our study differs from that of Madsen in that our patients had long-term renal failure and thus hyperplastic parathyroid glands. It is doubtful that hyperplasia was present in those patients with acute renal failure. A suppressant effect of oral $1,25(OH)_2D$ was also reported by Berl et al. (22) in 15 patients with chronic

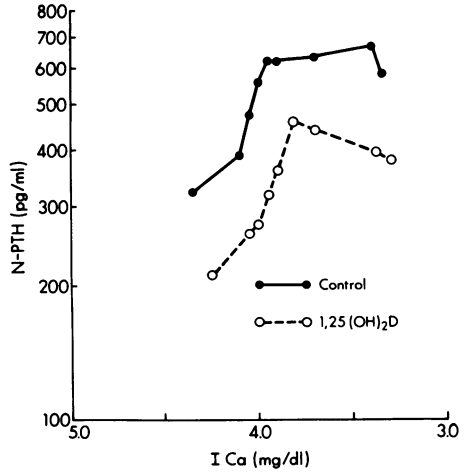


*Figure 7.* The response of PTH to hypocalcemic stimulation in patients with severe secondary hyperparathyroidism. There was an approximate doubling of PTH values during the control study (●) and after IV $1,25(OH)_2D$ (○). However, at every ICa level, the PTH levels were lower with $1,25(OH)_2D$.

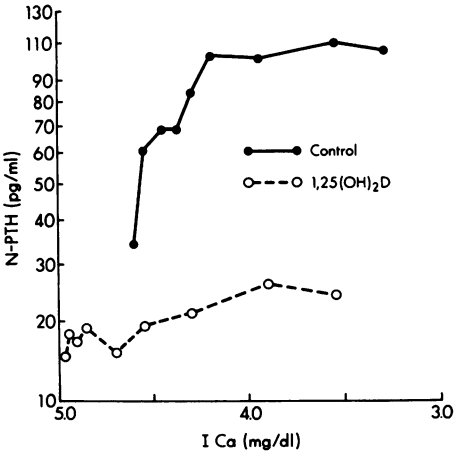


*Figure 9.* The response of PTH to hypocalcemic stimulation in patients with mild secondary hyperparathyroidism. (●) During the control dialysis PTH levels tripled. (○) After IV $1,25(OH)_2D$ the rise in PTH was blunted despite mean ICa values as low as 3.5 mg/dl.

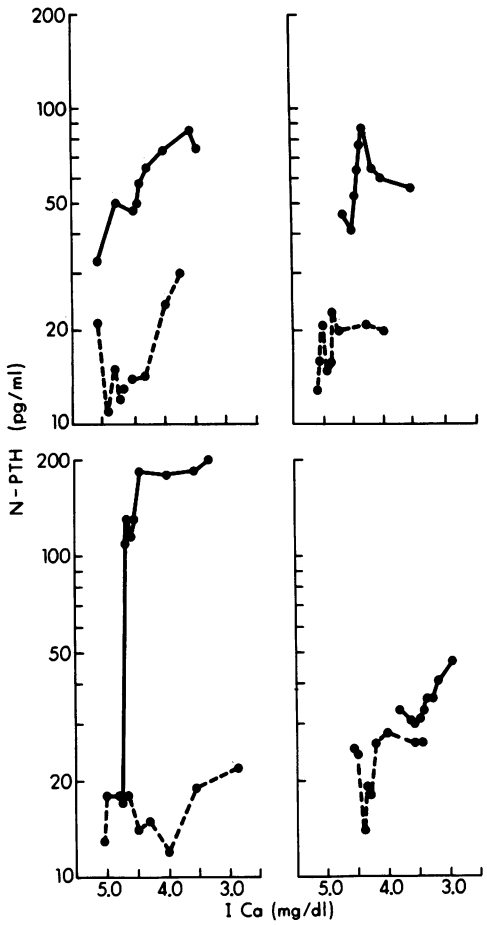


*Figure 10.* The responses of PTH to hypocalcemic stimulation in each of the subjects with mild hyperparathyroidism. (——) Control; (- - -) 2-wk IV $1,25(OH)_2D$.

renal insufficiency. They noted a 50% decline in PTH levels after 12 wk of treatment. However, there was also a marked increase in calcium levels during the study. Thus it was difficult to distinguish a direct effect of $1,25(OH)_2D$ from an indirect effect of calcium on the secretory function of the gland.

The results of the calcium infusion studies provide some insight into the mechanism of PTH suppression by $1,25(OH)_2D$. We found that the set point for PTH suppression by calcium fell from 5.24±0.14 to 5.06±0.15 mg/dl. Thus the gland appeared to be more sensitive to circulating calcium. These results are somewhat similar to those described by Oldham et al. (23) in vitamin D–deficient nonuremic dogs. When a slow calcium infusion was administered to the animals, no change in PTH levels were detected despite a 2 mg/dl increment in calcium values. However, when the dogs were pretreated with 1 μg of IV $1,25(OH)_2D$ 4 h before the calcium infusion, suppression of PTH by calcium was demonstrable. Goodman et al. (24) were unable to detect any changes in PTH levels in uremic children 24 h after 4 μg/70 kg of IV $1,25(OH)_2D$. Possibly, the absence of an acute PTH suppression in response to IV $1,25(OH)_2D$ reflected, in part, hyperplasia of the gland. In addition, Brown et al. (2) studied parathyroid tissue in vitro from patients with primary and secondary hyperparathyroidism and found that higher concentrations of calcium were required to suppress PTH secretion in both conditions compared to normal. Although our results suggest that the effect of $1,25(OH)_2D$ on the parathyroid gland is mediated, in part, by increased sensitivity to calcium, the cellular and subcellular mechanism for this phenomenon is subject to conjecture. Recent studies using cultured parathyroid cells and a cloned cDNA probe have shown that $1,25(OH)_2D$ in physiological concentrations decreased preproPTH and mRNA content in the cells (9). Further studies have revealed that this effect is primarily at the level of gene transcription (10). These findings have also been shown in vivo in the rat wherein preproPTH mRNA levels were < 4% of basal 48 h after 100 pmol of intraperitoneal $1,25(OH)_2D_3$ (11). Since Cantley et al. (8) found a close correlation between the decrease in PTH release and cellular preproPTH mRNA content, it is likely that $1,25(OH)_2D$ exerts its principal effect by decreasing the synthesis of PTH available for secretion. In that regard, it is of interest that the levels of PTH were the same, with or without $1,25(OH)_2D$, during the periods of maximal suppression by calcium. We interpret this finding as indirect evidence that two weeks of $1,25(OH)_2D$ does not affect parathyroid hyperplasia in those patients with severe secondary hyperparathyroidism. The continued high secretory rates, despite ICa levels as high as 6.0 mg/dl probably reflected nonsuppressible basal secretory rates of individual parathyroid cells in severely hyperplastic glands. On the other hand, the maximal PTH levels during hypocalcemic stimulation were lower after $1,25(OH)_2D$. Presumably, this represents a decrease in the storage pool of preproPTH available for secretion.

The response of the parathyroid gland to hypocalcemic stimulation in the presence or absence of $1,25(OH)_2D$ appeared to be different depending on the degree of hyperparathyroidism. In those patients with severe secondary hyperparathyroidism, the baseline PTH values fell by 38% after 2 wk of IV $1,25(OH)_2D$. During the induction of hypocalcemia there was an approximate doubling of PTH values in both groups with the curves running in a parallel fashion. Although it is hazardous to extrapolate in vivo data to intracellular events, these results are consistent with a lowering of intracellular content of PTH available for secretion. In those patients with mild secondary hyperparathyroidism, baseline PTH levels fell 44% from 32±6 to 18±3 pg/ml after IV $1,25(OH)_2D$. Although the ICa levels rose with IV $1,25(OH)_2D$, they remained within the normal range. During the control hypocalcemic stimulation, a threefold increase in PTH levels was seen. After IV $1,25(OH)_2D$, however, the induction of hypocalcemia led to minimal stimulation of PTH secretion. The peak concentrations of PTH, 26±5 pg/ml, remained less than twice those of control values despite a mean ICa value of 3.34±0.14 mg/dl. It appears, therefore, that the glands in mild hyperparathyroidism are more sensitive to the suppressant effects of short-term intravenous $1,25(OH)_2D$ than in those with high secretory rates. This is consistent with our unpublished observations that uremics with severe secondary hyperparathyroidism require more prolonged treatment with $1,25(OH)_2D$ compared to those with mild to moderate hyperparathyroidism. Whether the PTH response to hypocalcemia in the severely hyperparathyroid state would ultimately assume the blunted response of mild hyperparathyroidism during prolonged administration of intravenous $1,25(OH)_2D_3$ remains to be determined.

Although a reduction in the cellular content of preproPTH mRNA may play a role in explaining our findings, other mechanisms should be considered. Korkor (25) investigated the re-

ceptor binding of $1,25(OH)_2D$ in parathyroid glands obtained from uremic patients. When compared to those glands from patients with transplanted kidneys and patients with primary hyperparathyroidism, the receptor number was found to be decreased in uremia. Merke et al. (26) studied the parathyroid gland of rats 6 d after subtotal nephrectomy. As expected, the serum levels of $1,25(OH)_2D_3$ fell and the gland enlarged. Using competitive binding assays, they found a significant decrease in the specific binding capacity of the gland for $1,25(OH)_2D_3$ without changes in the affinity constant. Similar results have been reported by Brown et al. (27) in dogs with chronic uremia. In addition, $1,25(OH)_2D$ may exert its effect on PTH secretion by increasing the intracellular calcium content. Sugimoto et al. (28) studied effects of this steroid on cytosolic calcium in dispersed bovine parathyroid cells. Within 2 min of $1,25(OH)_2D$ exposure, intracellular calcium increased in a dose-dependent man due to an influx of extracellular calcium. These rapid effects of $1,25(OH)_2D$ were possibly attributable to a direct interaction with the parathyroid cell membrane. In addition, Merke et al. (29) recently studied the effect of $1,25(OH)_2D$ on parathyroid cell proliferation. Thymidine incorporation into the cells was studied 3 wk after partial nephrectomy or sham surgery. The uremic rats demonstrated marked enhancement of thymidine incorporation. The administration of intraperitoneal $1,25(OH)_2D$, however, reduced thymidine incorporation by 87%. To what extent our findings are a result of the above possible mechanisms is conjectural.

We have assumed in this study that changes in PTH levels, as measured by the amino-terminal antibody assay, reflects altered PTH secretion. Since the serum half-life of that portion of PTH is on the order of a several minutes (30), the values reflect recently secreted molecules. We cannot rule an effect of $1,25(OH)_2D$ on the degradation rate. However, this possibility appears unlikely since the steady state levels of amino-terminal PTH during maximal suppression by calcium were unchanged in the presence of $1,25(OH)_2D$.

Although it is likely that $1,25(OH)_2D$ directly suppresses the parathyroid gland in vivo, we cannot rule out the possibility that its effect is, in part, due to changes in aluminum metabolism. We have previously demonstrated (31) a direct inhibitory effect of aluminum on PTH secretion in dispersed bovine parathyroid cells. However, despite increasing the dose of oral aluminum and starting IV $1,25(OH)_2D$, we were unable to detect changes in aluminum levels. Thus, it appears unlikely that the effects of IV $1,25(OH)_2D$ were mediated through aluminum.

This study has demonstrated that $1,25(OH)_2D$ suppressed PTH levels in the absence of changes in ICa values. In part, these effects appear to be mediated by an increased sensitivity to calcium. Our findings have practical implications for the treatment of patients with chronic renal failure and severe secondary hyperparathyroidism. Intravenous $1,25(OH)_2D$ may be initially administered with a dialysis regimen containing a standard dialysate calcium concentration of 3.25–3.50 meq/liter. The goal of the maneuver should be to achieve predialysis calcium levels at the upper limits of normal and phosphorus concentrations between 4.5 and 5.5 mg/dl. However, if calcium levels rise to $> 11$ mg/dl, it would now appear that lowering the dialysate calcium concentration to $\sim 2.5$ meq/liter should be considered. This maneuver may prevent hypercalcemia and yet allow continued suppression of PTH secretion by $1,25(OH)_2D$. Sherman et al. (32) have found that a dialysate calcium concentration of 2.5 meq/liter is, in general, well tolerated. If IV $1,25(OH)_2D$ is instituted, careful monitoring of patients' serum calcium and phosphorus is mandatory. This is particularly important in patients taking large doses of calcium carbonate. We (16) and others (33–37) have shown that calcium carbonate is an effective phosphorus binder which does not carry with it the risks of aluminum overload seen with long ingestion of aluminum containing phosphorus binders. The current study provides a rational basis for the treatment of severe hyperparathyroidism in uremia without the attendant risk of hypercalcemia.

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