Calcitriol in the Management of Secondary Hyperparathyroidism of Renal Failure

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Secondary hyperparathyroidism (HPT) is characterized by persistent hypersecretion of parathyroid hormone (PTH), and produces characteristics of hyperparathyroid bone disease and a variety of biochemical and hormonal derangements. Management of uremic secondary HPT involves both prevention and treatment. Among preventive measures are attempts to control serum phosphate and serum calcium concentrations through dietary restriction, administration of phosphate binders, and calcium supplementation. Treatment with a vitamin D analog such as calcitriol returns plasma calcium concentrations toward normal and suppresses PTH secretion. The availability of a parenteral formulation of calcitriol, and new information regarding alternative routes of administration and regimens employing oral pulse dosing have renewed interest in calcitriol for the management of uremic secondary HPT.

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Summary

Hyperparathyroidism (HPT) is defined as the excess or inappropriate secretion of parathyroid hormone (PTH) associated with hyperplasia of the parathyroid glands. Secondary HPT associated with chronic renal failure results from long-standing chronic hypocalcemic stimulation and partial end organ resistance to the metabolic actions of PTH.[1] This condition occurs almost universally in patients with chronic renal failure in whom persistent hypersecretion of PTH can produce characteristics of hyperparathyroid bone disease, including osteitis fibrosa and osteosclerosis, and a variety of biochemical and hormone derangements that may in turn cause the dysfunction of other organ systems.[2–4]

The medical management of this disorder is multimodal and creates a constant challenge to the health care team. Practitioners are continually searching for new and innovative approaches to slow the progression of bone disease and improve patients' quality of life. A recent advance in this area is the use of newer dosing strategies for parenteral calcitriol.

Pathophysiology of Secondary HPT

The pathogenesis of secondary HPT is complex. Hypocalcemia, the recognized stimulus for the synthesis and secretion of PTH, is the product of several factors, including phosphate retention, decreased production of active vitamin D ($1,25\text{-}(OH)_2D_3$) secondary to decreased renal mass and hyperphosphatemia, reduced gastrointestinal absorption of calcium due to both decreased production of active vitamin D and depressed calcium transport in the uremic state, and peripheral resistance to the actions of PTH.[1–3, 5]

To understand the disturbances in mineral

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homeostasis, primarily calcium and phosphate, in patients with chronic renal failure, it is necessary to appreciate the interrelationships between PTH and 1,25-$(OH)_2D_3$, the control mechanisms involved in their synthesis and secretion, and their modes of action (Figure 1). In humans, the chief regulators of calcium homeostasis are PTH and 1,25-$(OH)_2D_3$. Parathyroid hormone is the principal hormone involved in the routine regulation of ionized calcium levels in the extracellular fluid, with 1,25-$(OH)_2D_3$ playing a key role in maintaining calcium balance. The two also exercise regulatory effects on each other. For example, PTH stimulates the production of 1,25-$(OH)_2D_3$ by activating the renal α-hydroxylase enzyme. Active vitamin D suppresses the synthesis and release of PTH by inhibiting PTH gene transcription through interaction with specific receptor proteins in target cells that have high affinity and specificity for 1,25-$(OH)_2D_3$.[6, 7] Active vitamin D enters the circulation and is transported by the vitamin D-binding protein to target tissues where it interacts with native receptors. The net result is that it augments the intestinal absorption of calcium and phosphorus from the diet. High levels of serum calcium in turn suppress PTH secretion by a feedback mechanism.[6, 8]

The kidneys lose a substantial portion of their ability to produce 1,25-$(OH)_2D_3$ in patients with uremia and reduced functional renal mass (Figure 2). This results in a decline in the intestinal absorption of calcium and eventual hypocalcemia. Hypocalcemia is further perpetuated by hyperphosphatemia, a direct consequence of decreased phosphate clearance.[9] Decreased clearance and subsequent accumulation of biologically active as well as inactive PTH fragments in the circulation also occur in renal impairment. Reduced clearance of other hormones such as catecholamines may contribute to excessive PTH secretion in secondary HPT through their ability to promote PTH production by an unknown mechanism.[3, 4]

In addition, the mechanisms that normally suppress PTH release are impaired. In individuals with normal renal function, a high serum calcium concentration acts as a trigger to suppress PTH synthesis and secretion. In uremic patients with hyperplastic parathyroid glands, the concentration of calcium necessary to suppress PTH secretion is higher (so-called shift in set point) since the parathyroids are relatively insensitive to negative feedback controls.[5]

Reduced availability of 1,25-$(OH)_2D_3$ and a

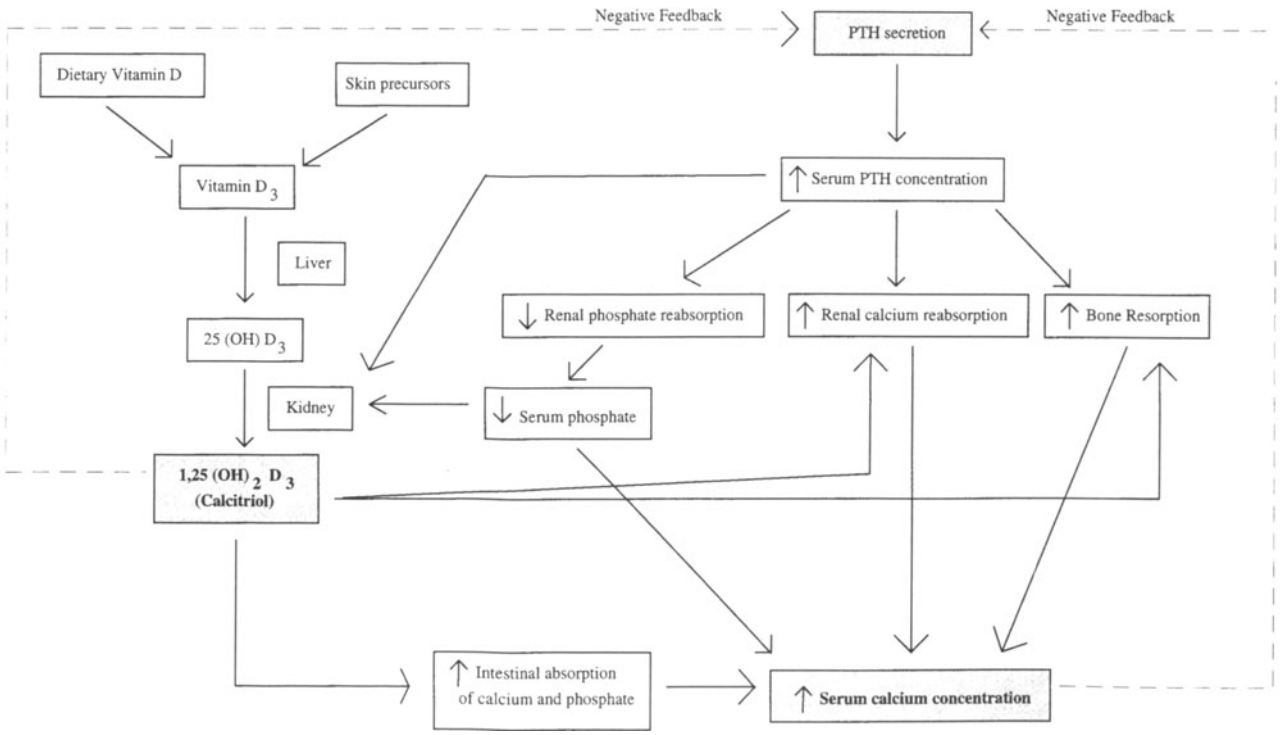

Figure 1. Parathyroid hormone axis regulation.

shift in calcium set point are the leading causes of impaired suppression of PTH secretion. Therefore, adequate suppression of PTH secretion may require high and potentially toxic serum calcium levels.[10] Peripheral resistance to the effects of PTH and the persistent stimulus of hypocalcemia leads to redirection of PTH activity to bone, causing the integrity of bone to be sacrificed in an effort to maintain normal levels of calcium.

The role of phosphate retention in the pathogenesis of secondary HPT was the subject of recent study. Phosphate accumulation in renal failure is known to contribute to HPT indirectly by causing hypocalcemia through 1,25-$(OH)_2D_3$ suppression and the reciprocal relationship with serum calcium concentrations. Reversal of hyperphosphatemia by dietary restriction, phosphate binders, and dialysis can therefore help correct hypocalcemia. Further evidence from a study in rats suggests that dietary phosphate restriction may suppress PTH secretion through a mechanism independent of 1,25-$(OH)_2D_3$ or serum calcium concentrations.[11] This reinforces the importance of dietary phosphate restriction and phosphate management in the treatment of this condition.

Conditions outside of the PTH axis can also contribute to the development or exacerbation of HPT in renal failure. Accumulation of aluminum can impair bone mineralization and contribute to the heterogeneity of the osteodystrophy that occurs in renal failure.[12] Traditionally, the most common source of aluminum intake in patients receiving dialysis was aluminum-containing phosphate binders, however, these are no longer recommended as first-line treatment of hyperphosphatemia. Thus, aluminum bone disease is much more rare now than in the past.[5] Metabolic acidosis has also been correlated with secondary HPT, and it has been suggested that correcting pH could help reduce PTH levels.[13]

Clinical Manifestations

Clinical manifestations of secondary HPT in renal disease vary depending on disease severity. Patients with renal failure typically have hypocalcemia and hyperphosphatemia. Bone pain, muscle weakness, pruritus, and skeletal abnormalities (renal osteodystrophy) are common.[12] The skeletal abnormalities include osteomalacia, generalized osteopenia, osteo-

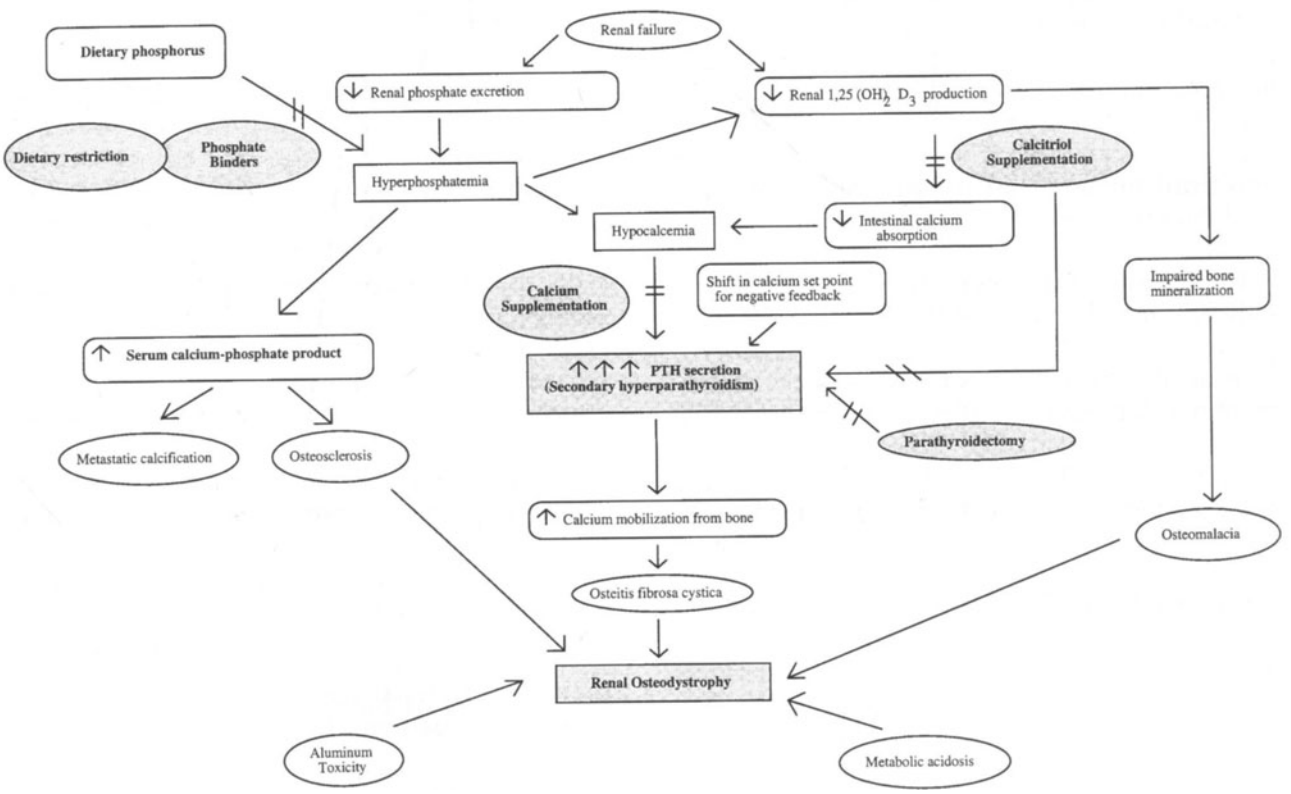

Figure 2. Pathophysiology and treatment of secondary hyperparathyroidism associated with renal failure.

sclerosis, and osteitis fibrosa cystica (increased osteoclastic resorption of the calcified bone with replacement by fibrous tissue). Skeletal pathology may reflect osteitis due to the excessive production of PTH in the initial stages of renal impairment. In later stages, effects of the impaired formation of 1,25-$(OH)_2D_3$ become more evident and osteomalacia predominates. Generalized osteopenia and subsequent pathologic fractures could also occur, particularly in patients undergoing long-term hemodialysis.[3, 12]

The most significant extraskeletal ramification of persistently elevated PTH levels is metastatic calcification. This is the end product of calcium-phosphate precipitation into arteries, joints, soft tissues and the viscera. It usually occurs when the calcium-phosphate product exceeds 72–80 mg/dl.[12, 13]

Diagnosis

Distinctly elevated levels of immunoreactive PTH (iPTH), electrolyte abnormalities such as decreased calcium and increased phosphate serum concentrations, and bone pain are early signs of parathyroid dysfunction. In addition, bone fractures, increased bone density observed on radiographs, bone biopsy, or bone scan; and elevations in serum alkaline phosphatase levels are all highly suggestive of secondary HPT.[12, 14, 15]

Parathyroid hormone exists in plasma as an intact 84-amino acid single-chain polypeptide hormone, and also as amino (N) terminal and carboxy (C) terminal hormone fragments. The biologic activity of PTH resides in its N terminal one-third portion. In peripheral plasma, the predominant form of iPTH is generally inactive and consists largely of C terminal fragments.[5]

To detect PTH levels in serum, various radioimmunoassays specific for the different segments of the hormone have been developed. The double-antibody or intact PTH radioimmunoassay measures the concentration of the whole polypeptide.[16] The N terminal, C terminal, and midregion immunoassays detect the concentrations of hormone fragments in serum.[3, 5] Debate continues as to which of these assays provides the most reliable assessment of parathyroid function.[3, 16–18] Consequently, the clinician should become familiar with the one performed locally, recognize its potential limitations, and interpret the results accordingly.

Management

Management of secondary HPT of chronic renal failure requires both prevention and treatment. The initial preventive focus is directed at maintaining serum calcium and phosphate levels within the normal range. In the face of fulminant disease, treatment requires reducing parathyroid mass and healing the bone disease and other complications.[1] If these measures fail to achieve a desirable outcome, parathyroidectomy is the definitive treatment. However, the availability of calcitriol is important in reducing the need for parathyroidectomy in these patients.[19]

It is essential to control serum phosphate levels to slow the progression of secondary HPT and, in turn, renal osteodystrophy and extraskeletal calcification. Restriction of dietary phosphate intake, administration of phosphate binders, and dialysis are generally employed to decrease phosphate retention in renal failure.[20–23] As mentioned, aluminum-containing phosphate binders are generally not prescribed as first-line agents, and calcium carbonate and calcium acetate are the phosphate-binding agents of choice. The chief limitation of these products is hypercalcemia, which can be offset by reducing the calcium content of dialysate solutions. Some authors recommend that standard dialysate concentrations of calcium should be lowered to accommodate the safe oral intake of calcium necessary for phosphate binding.[20]

Persistently low levels of serum calcium occur routinely in patients with chronic renal failure. Although calcium-containing phosphate binders rectify this problem somewhat, supplementation of dietary intake with elemental calcium 1.0–1.5 g/day may be necessary to maintain concentrations at or near the upper limit of normal, thus reducing the stimulus for PTH secretion. To reduce the risk of metastatic calcification, neither of these methods should be begun until the product of the calcium-phosphate serum concentrations is stabilized below 70 mg/dl.[24] Aluminum-containing phosphate binders may be given for a short time in conjunction with strict dietary phosphorus restriction and dialysis until the risk is reduced.

Calcitriol

The discovery that calcitriol (1,25-$(OH)_2D_3$) is produced by renal tissue, and the observation that uremic patients have low serum levels of 1,25-$(OH)_2D_3$, led to the conclusion that alterations in renal calcitriol synthesis, and therefore abnormalities in the vitamin D-PTH

axis, contribute to the pathogenesis of secondary HPT in patients with progressive renal failure.[10] In the past, calcitriol was administered to replace the loss of endocrine function and to treat persistent hypocalcemia.[3] The interaction of calcitriol with its intestinal receptors to promote the intestinal absorption of calcium, increase serum calcium levels, and reduce PTH synthesis and secretion is viewed as its indirect action.[25–27] Recently, interest has focused on the ability of calcitriol to suppress PTH production directly through interaction with receptors on the parathyroid glands. It is generally believed that many of the manifestations of secondary HPT can be reversed by treatment with vitamin D analogs, which are sterols with hypercalcemic and antirachitic activity. Reduced functional renal mass and the kidneys' inability to metabolize precursor products to active vitamin D effectively make calcitriol and 1-α-hydroxyvitamin D_3 the agents of choice in uremic patients. These agents require no metabolism by renal α-hydroxylase to become active.[25–27]

Two desired effects of calcitriol are returning plasma calcium concentrations to normal and suppressing PTH to levels slightly above (1.5–2.5 times) the upper limits of normal.[28] Lower levels may cause adynamic bone disease and predispose patients to deposition of aluminum on mineralized bone surfaces.[10, 29, 30] Low bone turnover rates also cause impaired bone formation by reducing the degree of microcallus formation; that is, the ability of the normal skeleton to repair bone damage and modify bone structure to various biochemical demands.[13]

Calcitriol was initially marketed is an oral dosage form (Rocaltrol; Roche Laboratories, Nutley, NJ). It received approval from the Food and Drug Administration for the management of hypocalcemia in patients receiving long-term renal dialysis. An initial dosage of 0.25 μg/day can be titrated until the desired effect is attained.[31] Interest in calcitriol for HPT secondary to renal failure was renewed because of the availability of a parenteral formulation and new information concerning alternative routes of administration and regimens. Parenteral calcitriol (Calcijex; Abbott Laboratories, Chicago, IL) has the same approved indication as the oral product, with a recommended initial dosage of 0.5 μg 3 times/week titrated to an optimum clinical effect.[32] The average wholesale price of oral calcitriol in 1995 was $1.04 for 0.25 μg and $1.66 for 0.5 μg. Parenteral calcitriol has an average wholesale price of $12.24 for 1.0 μg.[33]

Oral Administration

A number of studies reported the clinical usefulness and limitations of oral calcitriol in the treatment of secondary HPT.[34, 35] The minor PTH suppressive effect and symptom resolution with traditional daily doses of 0.25–1 μg are the result of increases in serum calcium concentration rather than a direct effect on PTH. Oral calcitriol also has a significant first-pass effect, with the primary site of metabolism being the gut.[36] Consequently, peripheral concentrations are reduced after oral administration when compared with intravenous administration.

The high frequency of hypercalcemic and hyperphosphatemic events associated with oral calcitriol secondary to its local action on the gut may also limit the application of this formulation.[37] However, some investigators attempted to take advantage of the hypercalcemic side effect and used the agent's indirect action to suppress PTH levels. High dosages (average 0.17–1.7 μg/day) were given to raise plasma calcium concentrations in 16 pediatric patients undergoing continuous ambulatory peritoneal dialysis (CAPD).[38] All patients were maintained on aluminum-containing phosphate binders in a dosage adjusted to maintain the serum phosphate below 6.0 mg/dl. The calcitriol dosages were actually within the recommended range for children, yet serum calcium concentrations increased significantly from a baseline of 9.9 ± 0.9 to 11.0 ± 0.6 mg/dl (2.4–2.8 mmol/L, $p<0.001$). Serum albumin concentrations averaged 3.3 ± 0.5 and 3.6 ± 0.5 g/dl at the beginning and end of the study, respectively (NS). Other changes were decreases in alkaline phosphatase from 530 ± 397 to 204 ± 551 IU/L ($p<0.01$) and in mid-region iPTH of 113 ± 131 μEq/ml ($p<0.005$). Baseline radiographic findings remained unchanged throughout the the study, indicating limited progression of renal disease and possible clinical benefit.

It was theorized that the general failure of oral daily calcitriol to return biochemical abnormalities of secondary HPT to normal was due to inadequate concentrations of calcitriol alone or in conjunction with insufficient dietary calcium supplementation.[39] Eight hemodialysis-dependent patients were given increasing dosages of calcitriol 0.5–1 μg/day until the serum concentrations exceeded 15 pg/ml (normal 10–50 pg/ml). Calcium carbonate was administered concomitantly with meals in an amount sufficient to titrate the serum calcium between 10 and 10.5 mg/dl (2.5–2.6 mmol/L).

Aluminum-containing phosphate binders were adjusted to maintain the serum phosphorus concentration between 3.0 and 6.0 mg/dl, and the dialysate calcium concentration was maintained at 3.5 mEq/L. Transient hypercalcemia caused temporary discontinuation of calcitriol in several patients. Reductions in intact PTH from 968 ± 176 to 365 ± 149 pg/ml ($p<0.05$) and serum alkaline phosphatase levels from 295 ± 65 to 97 ± 20 U/L ($p<0.05$) were seen after 15 months of therapy. No correlation to changes in clinical status was made.

To reduce the frequency of hypercalcemic events related to the agent while still achieving the high plasma concentrations required to cause direct suppression of PTH, 19 uremic patients received oral pulse calcitriol 4.0 µg twice/week for 6 months.[40] All patients were maintained on oral aluminum hydroxide to keep serum phosphorus concentrations between 4.0 and 6.0 mg/dl. Dialysate calcium concentrations were held constant at 3.5 mEq/L. Decreases in C terminal iPTH from 18.4 ± 2.6 to 9.6 ± 2.2 ng/ml ($p<0.001$) and alkaline phosphatase from 759 ± 203 to 270 ± 65 IU/L ($p<0.001$) occurred after 6 months of calcitriol therapy. Three patients experienced episodes of hypercalcemia (11.0–12.5 mg/dl, 2.74–3.1 mmol/L, albumin concentrations not reported) during the fourth month of the study. Symptoms (mostly gastrointestinal) and serum calcium levels were reduced after temporary discontinuation of calcitriol. Thus, high oral doses of calcitriol administered intermittently can cause partial reversal of PTH hypersecretion.

The reduction of iPTH (double-antibody method) was even greater, from 108 ± 13.8 to 44.1 ± 8.3 pmol/L ($p<0.01$), after administration of calcitriol 4 µg twice/week for 12 weeks to nine patients receiving long-term hemodialysis.[41] Details concerning calcium ingestion, use of phosphate binders, and dialysate calcium concentration were not reported. Differences in techniques of measuring PTH serum levels in these studies may account for the variations in PTH suppression.

Five patients receiving CAPD were administered oral calcitriol 5 µg twice/week for 6 months.[42] Calcium carbonate was continued as a phosphate binder throughout the study, and the dialysate calcium concentration was held at 3.5 mEq/L. Serum albumin levels did not change significantly during the study. Based on an overall 60% decrease in iPTH levels using various assays, the authors concluded that oral pulse therapy has a direct action on PTH levels and may be an option for the management of secondary HPT in patients who cannot tolerate large daily doses of calcitriol or who receive no substantial benefit from traditional daily regimens.

The timing of oral calcitriol administration may also influence the frequency and severity of hypercalcemia, possibly because less absorbable calcium is available for calcitriol-induced intestinal absorption at night than in the morning. The occurrence of hypercalcemia was lower in 35 hemodialysis patients who took daily doses of calcitriol at bedtime compared with the morning (50% and 80%, respectively; $p<0.01$).[43] Furthermore, the severity of the hypercalcemic events in patients receiving bedtime doses was less than that in patients given daily morning doses. These patients also received either calcium carbonate or calcium acetate as phosphate binders in equivalent phosphate-binding doses. Doses of calcium carbonate were about twice those of calcium acetate, yet no difference in the frequency of hypercalcemia was observed between the groups. These results agree with those of other studies comparing calcium carbonate and calcium acetate.[30]

In summary, success in achieving suppression of PTH depends on achieving relatively high serum calcitriol concentrations. Intestinal degradation of orally administered calcitriol and inadequate levels of the agent at peripheral sites are the major reasons why traditional daily doses fail to suppress PTH secretion adequately and halt progression of disease. Therapy is also limited by hypercalcemia and hyperphosphatemia due to the drug's local effects on the gastrointestinal tract. Development of hypercalcemia does not appear to be influenced by the calcium salt used for phosphate binding. However, a reduction of the dialysate calcium concentration may allow use of calcium-containing phosphate binders in association with pulse calcitriol.

Intravenous Administration

Intravenous calcitriol is a synthetic formulation that is available as a sterile aqueous solution for injection.[32] It was first given to patients who failed oral therapy. Potential advantages of the intravenous over the oral route are a reduced potential for hypercalcemia, higher peripheral calcitriol levels, and a greater potential for reducing PTH serum levels. The reduced hypercalcemic effect is thought to be due to a diminished local effect on the intestinal

absorption of calcium. Intravenous administration also negates intestinal metabolism and the loss of a substantial fraction of the drug before it reaches the general circulation. Blood levels are therefore higher than with oral dosing, resulting in higher calcitriol concentrations delivered to the parathyroid glands.[27, 37]

Twenty hemodialysis-dependent subjects received short-term, intermittent, intravenous calcitriol 0.5–4 μg 3 times/week after dialysis for 8 weeks.[36] The result was marked suppression of midregion and C terminal PTH levels of 70.1 ± 3.2% from baseline ($p \leq 0.001$). Serum calcium increased from a baseline mean of 7 to 9.4 ± 0.3 mg/dl (1.74–2.34 mmol/L), with related serum phosphate elevations. These findings suggest that intravenous calcitriol has a significant suppressive effect on PTH release and potential clinical utility in patients with secondary HPT. Mild hypercalcemic episodes may occur.

The effectiveness of long-term, intermittent, intravenous calcitriol infusions on bone disease associated with secondary HPT was evaluated in 12 hemodialysis patients with refractory disease who were under consideration for surgical parathyroidectomy.[44] Dosages of 1–2.5 μg 3 times/week were administered over an average of 11.5 months. Aluminum-containing phosphate binders were given to maintain serum phosphorus concentrations below 6.0 mg/dl. Neither oral calcitriol nor calcium was administered during the study; dialysate calcium concentrations ranged from 3–3.5 mM/L. Levels of iPTH, measured by either an N terminal or C terminal assay, decreased by a mean of 48% over the duration of the study, and serum calcium increased from 2.55 ± 0.03 to 2.67 ± 0.05 mmol/L (10.2–10.7 mg/dl, $p<0.01$). Serum phosphate concentrations remained relatively unchanged. The mean rate of bone formation was reduced 59% ($p<0.01$). Thirty hypercalcemic episodes (> 2.87 mmol/L, > 11.5 mg/dl) occurred in 10 patients, with 1 patient discontinuing therapy early due to persistent hypercalcemia. However, no patient reported symptoms related to hypercalcemia. The authors concluded that intravenous calcitriol lowers the rate of bone turnover by lowering serum PTH levels, thus decreasing the stimulus for bone resorption and bone stem cell (osteoblast) proliferation. This suppressive effect was documented in other studies.[10, 45–47]

In an attempt to avoid the hypercalcemia related to high doses, 21 hemodialysis-dependent patients with mild to moderate secondary HPT received low-dose intravenous calcitriol (mean maximum dose 0.92 ± 0.11 μg) after dialysis for 1–2 years.[48] Patients were given calcium carbonate with each meal in an amount adjusted to maintain serum phosphorus concentrations less than 6.0 mg/dl. Aluminum-containing phosphate binders were given only when the serum phosphorus exceeded 7.0 mg/dl. Dialysate calcium concentrations were maintained at 3.0 or 3.5 mEq/L. Calcitriol decreased N terminal iPTH to 48 ± 6% and 29 ± 5% of baseline values at 12 and 24 months, respectively ($p<0.0001$). Increases in serum calcium concentration over baseline were noted at 12 months (2.22 ± 0.04–2.41 ± 0.03 mmol/L, 8.9 ± 0.2–9.7 ± 0.1 mg/dl, $p<0.03$). No further elevations in calcium concentrations occurred with continued calcitriol therapy. With the exception of one patient, hypercalcemia did not affect calcitriol dosage adjustments. Serum phosphate concentrations remained unaltered. These findings suggest that low-dose intravenous calcitriol is effective in reducing PTH levels in patients with mild to moderate secondary HPT without causing significant hypercalcemia or hyperphosphatemia.

In contrast, significant hyperphosphatemic events occurred in 60% of 83 hemodialysis-dependent patients in a 4-month multicenter trial.[29] An initial dose of intravenous calcitriol 0.015 μg/kg was administered in conjunction with phosphate binders (aluminum salts, calcium carbonate, or a combination) to maintain serum phosphorus concentrations below 6.0 mg/dl. Reductions in intact PTH levels with this regimen were not statistically significant but were seen in 72% of patients. Baseline ionized calcium and alkaline phosphatase levels remained relatively unchanged throughout the study.

Low-dose intravenous calcitriol appears to result in few hypercalcemic events, but discrepancies concerning the degree of PTH suppression that occurs make its efficacy in the management of secondary HPT of renal failure questionable. Another major concern is the number of significant hyperphosphatemic episodes with this regimen in the face of adjuvant phosphate binders. Whether this strategy reduces the risk of prolonged suppression of bone turnover and subsequently lessens predisposition for adynamic or aluminum-related bone disease requires further study.

Despite all the clinical investigations, controversy remains regarding the optimum calcitriol dosage, the most effective route of administration, the effect of therapy on the

regression of parathyroid gland hyperplasia, and its long-term efficacy in patients with uremic hyperparathyroidism. To resolve these issues, the first randomized, double-blind, placebo-controlled comparison of oral pulse and intravenous calcitriol was conducted in 19 patients receiving hemodialysis over 36 weeks.[49] Although the protocol prescribed adjusting calcitriol from a starting dosage of 2 µg to a maximum of 4.0 µg 3 times/week, the maximum dosages administered averaged only 2.5 and 2.4 µg 3 times/week in the intravenous and oral arms, respectively. The development of hypercalcemia and refractory hyperphosphatemia precluded further increases. All patients received similar daily calcium supplementation and low dialysate calcium 1.25 mMol/L. Control of phosphate levels required progressive increases in phosphate-binding capacity of 61% and 117% over controls in the intravenous and oral groups, respectively, administered in the form of calcium carbonate or aluminum hydroxide, although 70% of patients in the former and 100% in the latter group experienced at least one hyperphosphatemic episode. Hypercalcemic episodes occurred in 80% and 56% of subjects, respectively. The frequency of hyperphosphatemic and hypercalcemic events was not considered to be significantly different between groups.

The investigators also noted that at the maximum tolerated dosage of calcitriol, serum 1,25-dihydroxyvitamin D levels were significantly greater 60 minutes after intravenous (389 pmol/L) than after oral administration (128 pmol/L),[49] yet no significant difference in the overall degree of PTH suppression was observed (maximum average reduction 43%, p=0.016). Neither route caused significant reduction in average parathyroid gland volume or number despite the substantial decline in PTH levels. The authors concluded that the two routes of administration were equivalent in the treatment of uremic secondary HPT. Hyperphosphatemia and hypercalcemia severely limited the upward titration of calcitriol dosages, and may therefore have limited the potential for therapeutic effects. The results also challenge the finding of fewer hypercalcemic events associated with intravenous calcitriol reported by others.[27, 36, 37, 48]

Intravenous calcitriol is a safe and effective means to suppress parathyroid gland secretion, reduce serum PTH, and lessen the rate of bone turnover in uremic patients with secondary HPT. Undesirable effects such as hypercalcemia and hyperphosphatemia can occur, however. Whether the magnitude of these effects is markedly reduced compared with oral calcitriol therapy is still a topic of debate.

Other Routes of Administration

With the increasing use of CAPD and continuous cycling peritoneal dialysis (CCPD) for the management of uremic patients, effective and convenient alternatives to intravenous calcitriol are necessary. Intraperitoneal, subcutaneous, and intramuscular routes of calcitriol administration have been investigated in this patient population. These alternative routes are believed to be other methods by which the intestinal degradation of calcitriol is bypassed, allowing for heightened delivery of the agent to peripheral target tissues.[45, 50]

Continuous ambulatory peritoneal dialysis causes only small fluctuations in PTH levels, even with its removal of PTH and the maintenance of calcium in the upper limits of normal with oral calcitriol. It was hypothesized that PTH suppression could be accomplished better by increasing calcium absorption from the dialysate (calcium mass transfer) with higher dialysate concentrations of calcium.[5, 51] In addition, intraperitoneal administration of calcitriol could augment the PTH suppressive effect by delivering high serum levels of calcitriol to the periphery.

To test the plausibility of the hypothesis and to determine the effects of intraperitoneal calcitriol on PTH levels, 11 patients received CAPD with a standard dialysate containing 3.5 mEq/L calcium for a 2-month control period. After this they received dialysis with a dialysate fortified to calcium 4.0 mEq/L for another 2 months. Calcium absorption was increased with the fortified dialysate compared with the standard one (84 ± 6.2 vs 37.8 ± 16.9 mg/day), however, no changes in ionized calcium levels were observed. Modest suppression of PTH levels to 84% of control values ($p<0.05$) was also reported with the calcium-fortified dialysate.

Intraperitoneal calcitriol 0.5–2 µg/day was subsequently administered in 2 L dialysate containing either 4.0 or 3.5 mEq/L calcium/day to the 11 patients for 3 months.[50] With the institution of intraperitoneal therapy, increases in ionized calcium levels from 5.31 ± 0.09 to 10.5 ± 0.17 mg/dl (1.32–2.62 mmol/L) and corresponding decreases in serum PTH levels to 53.9 ± 7.9% of control values ($p<0.01$) occurred. Thus, the primary effect of intraperitoneal calcitriol on

PTH levels could be attributed to elevations in serum calcium concentrations.

Loss of calcitriol due to interaction with the peritoneal dialysis delivery system is a major disadvantage associated with the intraperitoneal route. Two in vitro studies infused radiolabeled calcitriol admixed with dialysate into standard dialysate bags and tubing and then immediately drained the dialysate. Although this procedure was done to minimize contact time, only 62–63% of the dose was delivered through the system.[50, 52] Longer periods of contact resulted in even greater loss of calcitriol, with 26% remaining at 20 hours.[52]

A pharmacokinetic comparison of intraperitoneal, oral, and intravenous routes of administration confirmed these findings. Six adolescent peritoneal dialysis-dependent patients received a one-time dose of calcitriol 60 ng/kg.[50] The bioavailability of intraperitoneal calcitriol was 66% of that after intravenous administration and essentially equivalent to that after oral administration. Although direct instillation of injectable calcitriol into the peritoneal cavity would be expected to minimize this interaction, no improvement in bioavailability was found.[50] A 2-fold increase in the intraperitoneal dose of calcitriol (120 ng/kg) resulted in bioavailability comparable with that of an intravenous dose of 60 ng/kg. The similarity in the percentage of delivered drug in the in vitro and in vivo studies leads one to conclude that intraperitoneal bioavailability is explained by the adherence of calcitriol to the plastic materials of the dialysis system, although it was suggested that the agent could also be lost through metabolic and degradatory processes after intraperitoneal administration.[50]

Due to the bioavailability problems associated with intraperitoneal administration, subcutaneous administration was proposed as an alternative parenteral route for patients receiving peritoneal dialysis. A one-time dose of 2 μg resulted in peak serum concentrations 1 hour after administration,[53] and mean serum concentrations persisted above baseline levels for 24 hours.

Seven uremic patients receiving CAPD who had severe secondary HPT were given subcutaneous calcitriol 2 μg 3 times/week for 8 weeks.[54] On average, a 55% reduction in intact PTH levels was noted from baseline (349 ± 26–158 ± 20 pg/ml, $p<0.04$). In the five patients with reduced PTH levels there was an inverse relationship between plasma PTH and calcium levels at week 6. The suppression of PTH was believed to occur secondary to elevated levels of calcium, although a direct effect could not be ruled out.

Uremic pediatric patients had persistently elevated PTH levels and recurrent episodes of hypercalcemia after a period of oral calcitriol administration and calcium supplementation.[45] Intramuscular calcitriol 10.5–16.9 ng/kg (0.375–1.2 μg) 3 times/week for up to 6 weeks reduced alkaline phosphatase activity 51–59% and PTH levels 47–51%.

The intraperitoneal, subcutaneous, and intramuscular routes of calcitriol administration are promising for the management of secondary HPT in renal failure. However, they must be compared directly with the oral and intravenous routes.

The Role of Calcitriol in the Management of Renal Osteodystrophy

The place of calcitriol and the timing of its administration (prevention vs therapy) in the progression of renal osteodystrophy remains unclear. Some investigators advocate early administration in patients with moderate renal impairment, even in those with no symptoms, normal serum alkaline phosphatase concentrations, and normal bone radiographs. They argue that if calcitriol therapy is delayed, PTH hypersecretion may never be reversed since the hyperplastic parathyroid glands will continue to secrete supraphysiologic concentrations of PTH.[10, 47, 55]

A prospective, double-blind, controlled trial of oral calcitriol was conducted in 16 patients with creatinine clearances of 20–59 ml/minute.[55] Although biochemical and radiologic markers of renal osteodystrophy were within normal limits, all patients had abnormal bone histology. Most received calcitriol 0.25 μg/day; those receiving 0.5 μg/day were likely to require a dosage reduction due to hypercalcemia. Treatment for 12 months resulted in a significant reduction in alkaline phosphatase within the normal range and an insignificant reduction in C terminal PTH levels. There were significant reductions in indexes of bone formation and resorption and in the number of osteoblasts.

The finding of reduced bone formation is of concern, since the goal of therapy is to bring rapid bone turnover back to normal, not to cause adynamic bone disease. It was suggested that smaller dosages of 0.25 μg/day or an intermittent schedule with 1 month on and 1 month off could

alleviate the suppression of bone formation that sometimes results with this drug.[56]

Another area of concern in patients in early stages of renal disease is the potential for calcitriol's deleterious effects on renal function.[57] An early trial reported a more rapid decline in renal function after several months of therapy compared with changes seen before therapy.[58] More recent reports failed to document any deleterious effects on renal function, despite episodes of prolonged hypercalcemia, which have the potential to cause more rapid progression of renal failure.[59, 60] These findings are encouraging, and with careful monitoring and a modest dosage in the range of 0.25 µg/day, calcitriol may prevent progression of renal bone disease in patients with mild to moderate renal impairment.

The agent has beneficial effects in patients with end-stage renal failure with no overt evidence of bone disease.[61] The success of oral or intravenous high-dose pulse therapy is apparent, although some believe that the risk of adynamic bone disease associated with calcitriol can be avoided by giving calcium carbonate alone in high dosages (6 g/day) or in conjunction with reduced calcium dialysate as first-line treatment. One group advocates such an approach, reserving vitamin D_3 derivatives for patients with more severe disease when iPTH levels exceed twice the upper limit of normal.[30] Clearly, comparative trials must assess the efficacy of the various prophylactic regimens.

New Vitamin D Analogs

Since the hypercalcemic effect of oral calcitriol may preclude its use in the management of secondary HPT, the search continues for new vitamin D analogs that have suppressive effects on the parathyroid glands without increasing intestinal calcium absorption.[12] One analog of calcitriol currently under clinical investigation is 19-nor-1,25-$(OH)_2D_2$. This agent exhibited potent suppressive effects on PTH secretion in rats, with low calcemic and phosphatemic activity compared with calcitriol.[62] This noncalcemic analog may be effective in the treatment of secondary HPT, providing another option for patients who cannot tolerate calcitriol.

Other noncalcemic vitamin D analogs that have been isolated include the 24-homo D_3 analogs MC903, 22-oxacalcitriol, and 1,25-$(OH)_2$-16-ene-23-yne-D_3.[63, 64] To date, the therapeutic effects of these compounds have been assessed only in animal trials.

Summary

Many questions regarding calcitriol and its efficacy in the management of secondary HPT remain unanswered. These lingering questions are due in part to lack of understanding of the pathogenesis of that disorder in patients with renal failure. Based on the available literature, intravenous administration appears to be the most promising because of its ability to deliver high calcitriol levels to the periphery and subsequently suppress PTH. Although all of the routes of administration are associated with some degree of hypercalcemia, the intravenous route may cause the fewest hypercalcemic effects. When intravenous therapy is not feasible, oral pulse therapy is an option. It can be administered at night or other times of low calcium ingestion to reduce the potential for hypercalcemia. There is little documentation of the intraperitoneal, subcutaneous, and intramuscular routes.

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