Treatment of secondary hyperparathyroidism by intravenous calcitriol

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Introduction

Secondary hyperparathyroidism resulting in osteitis fibrosa is the most common bone abnormality observed in dialysis patients. Most recent data strongly suggest that a deficit of calcitriol is an important factor in the high parathyroid hormone (PTH) levels of these patients[1-2]. Thus, it is not surprising that the administration of calcitriol orally[3-4] has resulted in the amelioration or even dramatic improvement of secondary hyperparathyroidism. What makes the use of intravenous calcitriol an attractive modality of therapy is the recent observation that calcitriol per se, in the absence of hypercalcemia inhibit both synthesis and secretion of PTH[5-6]. In the present discussion we will briefly review the physiological action of calcitriol in dialysis patients in regard to divalent ion metabolism, then we will discuss new data on calcitriol and PTH interaction and finality, the available clinical data on the intravenous use of calcitriol will be reviewed.

Effects of calcitriol in end stage renal failure

There are several important effects of calcitriol in the uremic patient. It is these important biological effects what makes the use of calcitriol essential in the control of secondary hyperparathyroidism. First, it is well known that intestinal absorption of calcium is primarily dependent on calcitriol[7]. Thus, in several studies the administration of calcitriol to patients with renal insufficiency always result in a marked increase of the low gut absorption of calcium[8]. Likewise, intestinal absorption of phosphate also augments after calcitriol therapy[9]. However, the magnitude of this increment in lower than that observed with calcium. A third major effect of calcitriol is to increase serum calcium from the hypocalcemic range to normo or hypercalcemic range. Although this increment may be due to a multifactorial action of calcitriol, by far the increase in intestinal absorption of calcium is the major factor. Of interest is the fact that the rise in serum calcium may not occur for weeks, even months after commencement of calcitriol therapy[10], even though intestinal calcium absorption may be increased and calcium balances are positive. This may reflect active bone mineralization and marked movement of calcium from the extracellular to the intracellular space.

For years it has been known that calcitriol administration is followed by a decrease in PTH levels. However, until recently, this inhibitory effect of calcitriol on PTH was thought to be secondary to the ensuing hypercalcemia. However, as we will discuss shortly, a direct inhibitory effect of this sterol on PTH secretion may be its most important biological effect in the uremic patient.

Finally, various studies using both oral and intravenous calcitriol have shown marked improvement in the osteitis fibrosa observed in the bone histology of dialysis patients. However, it should be remembered that in a substantial number of patients, bone histology does not always return to normal, clearly indicating the presence of factors other that calcitriol in the pathogenesis of secondary hyperparathyroidism.

Vitamin D and PTH interactions

Historically, an increase plasma following calcitriol were thought to be the only mechanism influencing PTH secretion and improving the secondary hyperparathyroidism observed in dialysis patients. However, recent studies have shown calcitriol to decrease PTH gene transcription in the rat[11] and in primary cultures of parathyroid gland cells[11, 12]. In the past, it had been assumed that the decrease in PTH secretion observed in dialysis patients treated with Vitamin D was the result of the ensuing hypercalcemia. New studies in dialysis patients demonstrate a direct inhibitory effect of calcitriol on PTH secretion.

Very recent studies have evaluated the regulation of parathyroid cell gene expression in experimental uremia[13]. The effect of calcitriol on PTHmRNA in doses as low as 25 mmol/100 g body weight decreases significantly with no greater effect at 100 pmol/100 g, unlike in normal rats. Neither hypo or hypercalcemia seemed to change

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PTHmRNA. The explanation for this lack of response is unclear, but it is likely that the prevailing levels of calcitriol may determine the response of the parathyroid gland to changes in Ca concentration.

Silver et al. recently demonstrated a suppressive effect of calcitriol on cytoplasmic mRNA coding for preproparathyroid hormone in isolated parathyroid cells[5]; They have recently shown *in-vivo* in the rat that calcitriol decreases PTH gene transcription by more than 90 % after a single injection of 100 pmol[11]. Similar results have been observed *in-vitro* in primary cultures of parathyroid cells[6].

Slatopolsky et al. compared the effects of oral and intravenous administration calcitriol on the circulating plasma levels of calcitriol as well as on PTH secretion[14]. They observed that oral administration of calcitriol in doses adequate to maintain serum calcium in the upper limits of normal did not alter PTH levels, whereas a marked suppression (70.1 ± 3.2 %) of PTH levels was observed in all 20 patients receiving intravenous calcitriol. The studies by these authors suggest that a 20.1 ± 5.2 % decrease in PTH resulted with administration of IV calcitriol without significant changes in serum calcium. However, by the second month of therapy, hypercalcemia developed as PTH secretion decreased. Thus, the possibility that hypercalcemia per se may also have been a factor in the PTH suppression could not be ruled out.

Delmez et al. evaluated the inhibitory effect of intravenous calcitriol on PTH synthesis in uremic patients undergoing maneuvers designed to avoid changes in serum calcium concentration[15]. In addition, the response of the parathyroid gland in patients undergoing hypercalcemic suppression and hypocalcemic stimulation of PTH before and after two weeks of intravenous calcitriol was evaluated. In patients undergoing hypercalcemic suppression, PTH values fell from 376 ± 66 to 290 ± 50 pg/ml after calcitriol administration. During hypercalcemic suppression, the set point of Ca for PTH secretion fell from 5.25 ± 0.14 to 5.06 ± 0.15 mg/dl after calcitriol. A similar decline in PTH levels using intravenous, administration of calcitriol was noted in those patients undergoing hypocalcemic stimulation of PTH. The authors concluded that intravenous calcitriol directly suppresses PTH secretion in the uremic patient, and this suppression in part was due to increased sensitivity of the gland to ambient plasma calcium levels.

Recently, we have evaluated the direct inhibitory effect of calcitriol on parathyroid function in dialysis patients with secondary hyperparathyroidism[16]. Following a baseline evaluation of parathyroid function, we administered 2 μg of calcitriol intravenously after dialysis three times weekly for 10 weeks. Parathyroid function was assessed by inducing hypo- and hypercalcemia using a low and a high Ca dialysate during two separate dialysis performed a week apart. In order to avoid hypercalcemia during calcitriol administration, the dialysate calcium concentration was reduced to 2.5 mEq/l.

Parathyroid hormone values after dialysis induced hypo and hypercalcemia were plotted against serum ionized calcium for each patient, and the sigmoidal relationship between PTH and calcium was evaluated. A sigmoidal relationship was established for each patient and the true set point of calcium (i.e. the level of serum calcium which induces a 50 % inhibition of maximal PTH stimulation) was determined. The basal PTH levels fell from 902 ± 126 pg/ml to 466 ± 152 pg/ml ($P < 0.01$) after 10 weeks of calcitriol therapy. This occurred in the absence of any significant change in serum calcium concentration. The serum ionized calcium/PTH sigmoidal curve shifted to the left and downward after calcitriol therapy. Thus, the maximum PTH response during hypocalcemia decreased after calcitriol therapy from 1,661 ± 485 pg/ml to 1,031 ± 280 pg/ml ($P < 0.05$).

The slope of the sigmoidal curve changed from −2125 ± 487 to −1563 ± 385 ($P < 0.05$). The set point of ionized calcium (4.6 ± 0.11 at baseline vs 4.4 ± 0.07 mg/dl at 10 weeks) did not change significantly with calcitriol therapy. However, if one patient with severe hyperphosphatemia was excluded from the study, there was a statistically significant change in the set point of calcium after calcitriol therapy. In summary, 10 weeks of intravenous calcitriol therapy decreased PTH secretion across a wide range of serum ionized calcium concentrations, shifting the ionized calcium/PTH sigmoidal curve toward normal (left and downward). Most likely, the set point of calcium also changed. There were no significant changes in basal serum calcium concentration throughout the study. These results clearly demonstrate a direct, inhibitive effect of intravenous calcitriol on parathyroid function in dialysis patients with secondary hyperparathyroidism.

Clinical effects of intravenous calcitriol

Preliminary data from Norris et al., demonstrated the beneficial effect of intravenous calcitriol in 10 patients with overt secondary hyperparathyroidism[17]. These investigators administered 1-5 μg calcitriol intravenously to the patients three times per week following each dialysis for 13 months. They observed a decrease in PTH levels of 42 ± 4 %, an increase in serum calcium from 10.1 to 11.2 ± 0.1 mg/dl and a 62 ± 4 % decrease in serum alkaline phosphatase.

Andress et al., showes the beneficial effect of intravenous calcitriol on the bone lesion of secondarty hyperparathyroidism[18]. These authors evaluated 12 hemodialysis patients with significant osteitis fibrosa who were refractory to conventional oral calcitriol therapy. They receiver 1-2.5 μg of calcitriol intravenously three times a week. After one year of therapy, an increase in serum ionized calcium was observed from 2.5 to 2.6 mmol/l and a decrease in PTH from 172 ± 34 to 69 ± 16 pg/l. Most importantly, there was a significant improvement in bone histology after one year of calcitriol therapy.

Hamdy et al., evaluated the effect of intravenous calcitriol in four patients with persistent hypercalcemia and

marked secondary hyperparathyroidism[19]. These patients had been shown to be intolerant to oral administration of calcitriol. After each dialysis, calcitriol was administered intravenously in doses of 0.5-2.5 μg for 2 months. Calcitriol therapy continued for 7 and 8 months respectively, in 2 of the 4 patients. After 2 weeks of therapy, a significant decrease in serum calcium was observed which was maintained throughout treatment as IV calcitriol dosage was increased. This was associated with a decrease in serum of PTH. During the long-term administration of calcitriol, serum calcium values increased but lower concentrations of PTH were maintained. The authors concluded that the increment in serum calcium was not a prerequisite for the suppression of PTH secretion by calcitriol and that the presence of hypercalcemia does not preclude the use of intravenous calcitriol.

Similar observations have been made of the effect of intravenous 1-alphahydroxy-D_3 (1a(OH)D_3) on secondary hyperparathyroidism in chronic uremic patients undergoing maintenance dialysis. Brandi et al., evaluated the effect of this sterol on PTH levels in 21 patients on chronic hemodialysis[20]. The patients were treated for 3 months with increasing dose of 1a(OH)D_3 while serum calcium was carefully controlled. The sterol was given intravenously at doss of up to 4 μg three times a week, and blood samples were obtained weekly. After 3 months, intact PTH levels were reduced by an average of 67 ± 6 % serum calcium was kept within normal levels hut there was a net increase from 1.17 to 1.30 mmol/l. The authors concluded that although high normal levels of Ca may have influenced PTH secretion, an effect of the alpha sterol, independent of serum calcium concentration was also observed. This effect, they added, may mediated by calcitriol an 1a(OH)D_3 is converted in the liver into calcitriol by the enzyme 25-hydroxylase is assumed. Another possibility is that the parathyroid gland may possess receptors for 1a(OH)D_3 with an effect similar to that of calcitriol receptors.

In summary, although the beneficial effect of intravenous calcitriol is apparent, it is difficult at present to reach any conclusion with regard to its overall therapeutic role in dialysis patients. Before final recommendations are possible, certain issues have to be elucidated, such as the net effect of higher plasma calcitriol levels observed with intravenous calcitriol therapy as compared to intravenous therapy, and the effect of a given plasma level of calcitriol on target organs which can be achieved by oral versus intravenous administration. In our opinion, patients who may benefit from intravenous calcitriol are: 1) The noncompliant patients who are not taking oral calcitriol. 2) The patient with overt hyperparathyroidism who cannot be treated with oral calcitriol therapy because of induced hypercalcemia. In the past, this type of patient has surgical parathyroidectomy. Theoretically, it is conceivable that sufficient intravenous calcitriol may induce a medical rather than a surgical parathyroidectomy. 3) The patient who develops hyperphosphatemia immediately after oral administration of calcitriol may respond to intravenous calcitriol with a lesser degree of hyperphosphatemia. 4) Those patients with severe fibrosa who must undergo parathyroidectomy to ameliorate bone abnormalities may benefit from intravenous calcitriol prior to parathyroidectomy[22]. In the post-parathyroidectomy period, hypocalcemia may be accompanied by high morbidity and mortality because of tetany and bone fractures. In these patients, administration of intravenous calcitriol one or two weeks prior to parathyroidectomy may render them less prone to severe hypocalcemia and decrease morbidity and mortality.

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