Synergistic Effect of Cinacalcet and Active Vitamin D in a Dialysis Patient With Secondary Hyperparathyroidism

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ABSTRACT: While treating a long-term dialysis patient for secondary hyperparathyroidism (SHPT), indications of a synergistic effect between cinacalcet HCl and active vitamin D were observed. After 2.5 years, high initial cinacalcet doses of 180 mg/day could be significantly reduced to only 30 mg/non-dialysis day without losing control over the intact parathyroid hormone. Calcium-phosphorus product improved over time. The combination of cinacalcet and active vitamin D may improve the treatment of SHPT in dialysis patients.

Long-term dialysis patients frequently suffer from secondary hyperparathyroidism (SHPT), which develops from increased phosphate retention and reduced renal production of active vitamin D.[1] As a consequence, uremic bone disease and vascular calcification may develop. To control intact parathyroid hormone (iPTH) and phosphorous, most dialysis patients receive vitamin D and phosphate binders, however, an increase of vitamin D doses is often limited by hypercalcemia, which is expected to lead to an increased vascular calcification and an associated increased mortality. Currently, only a few patients meet the target ranges for iPTH, calcium (Ca), phosphorous (P), and calcium-phosphorus product (Ca × P) as recommended by the KDOQI guidelines.[2,3]

In the case of uncontrolled autonomous iPTH production, resection of the parathyroid glands is standard therapeutic procedure so far. Surgery, however, is associated with the risk of vocal cord paresis, an increased risk of low bone turnover, and bone fractures.

In 2004, the calcimimetic drug cinacalcet HCl[4] became available providing a new and independent mechanism in controlling iPTH.[5-8] Cinacalcet activates the Ca-sensing receptor of parathyroid cells through allosteric modification and increases the sensitivity of the membrane-bounded calcium receptor to extracellular calcium. Cinacalcet post-transcriptionally decreases iPTH gene expression by reducing mRNA stability.[1] As a consequence, iPTH and Ca are reduced. In contrast, active vitamin D decreases iPTH mRNA transcription in the parathyroid cells via the cytoplasmic vitamin D receptor.[1] As cinacalcet and active vitamin D act at different points of the iPTH expression pathway, the combination of both may provide a new therapeutic option in the treatment of SHPT in dialysis patients.

Up until now, however, the optimal treatment algorithm regarding cinacalcet plus vitamin D versus cinacalcet alone is not clear.[7,9-11] Here, we report on a dialysis patient in whom we found indications of a synergistic effect of cinacalcet and active vitamin D.

Case Report

We present the case of a 42-year-old male, long-term dialysis patient with hypoplastic kidneys as the primary disease. The patient had been treated with hemodialysis since 1982, with a break in therapy during which he had a transplant between 1986 and 1992, after which hemodialysis was resumed. Early therapy for SHPT included oral vitamin D replacement with cholecalciferol and in the early 1990s the patient was switched to active vitamin D (calcitriol). Phosphorus levels were controlled by calcium carbonate and later additionally by the calcium-free phosphate-binding drug sevelamer. Within the reported period, calcidiol blood levels were determined only twice (30.0 ng/mL in 7/2003 and 9.2 ng/mL in 2/2008).

At the beginning of 2004, the patient's iPTH increased to 450 pg/mL (*Figure 1A*). In spite of high doses of calcitriol, the iPTH continued to climb to 814 pg/mL (*Figure 1B*). At the end of 2004, the calcimimetic drug cinacalcet became available and was given to the patient. The target for iPTH was 150 to 300 pg/mL as recommended by the KDOQI guidelines.[3] Within a period of 11 weeks, the cinacalcet doses were increased from 30 to 120 mg/day; 13 months after initiation, the cinacalcet dose was further increased to 180 mg/day. Within 7 weeks after initiation of cinacalcet, iPTH decreased to around 300 pg/mL (*Figure 1A*).

At this point, we assumed that the iPTH was controlled primarily with cinacalcet, so we halved the calcitriol dose 14 weeks after initiation of cinacalcet. After the calcitriol dose was reduced, there was an immediate increase in iPTH to 685 pg/mL (T_1 in *Figure 1A,B*). We therefore adjusted the calcitriol dose to the previous level and iPTH decreased again to below 300 pg/mL. The rapid change of ➲

DOI: 10.1002/dat.20405

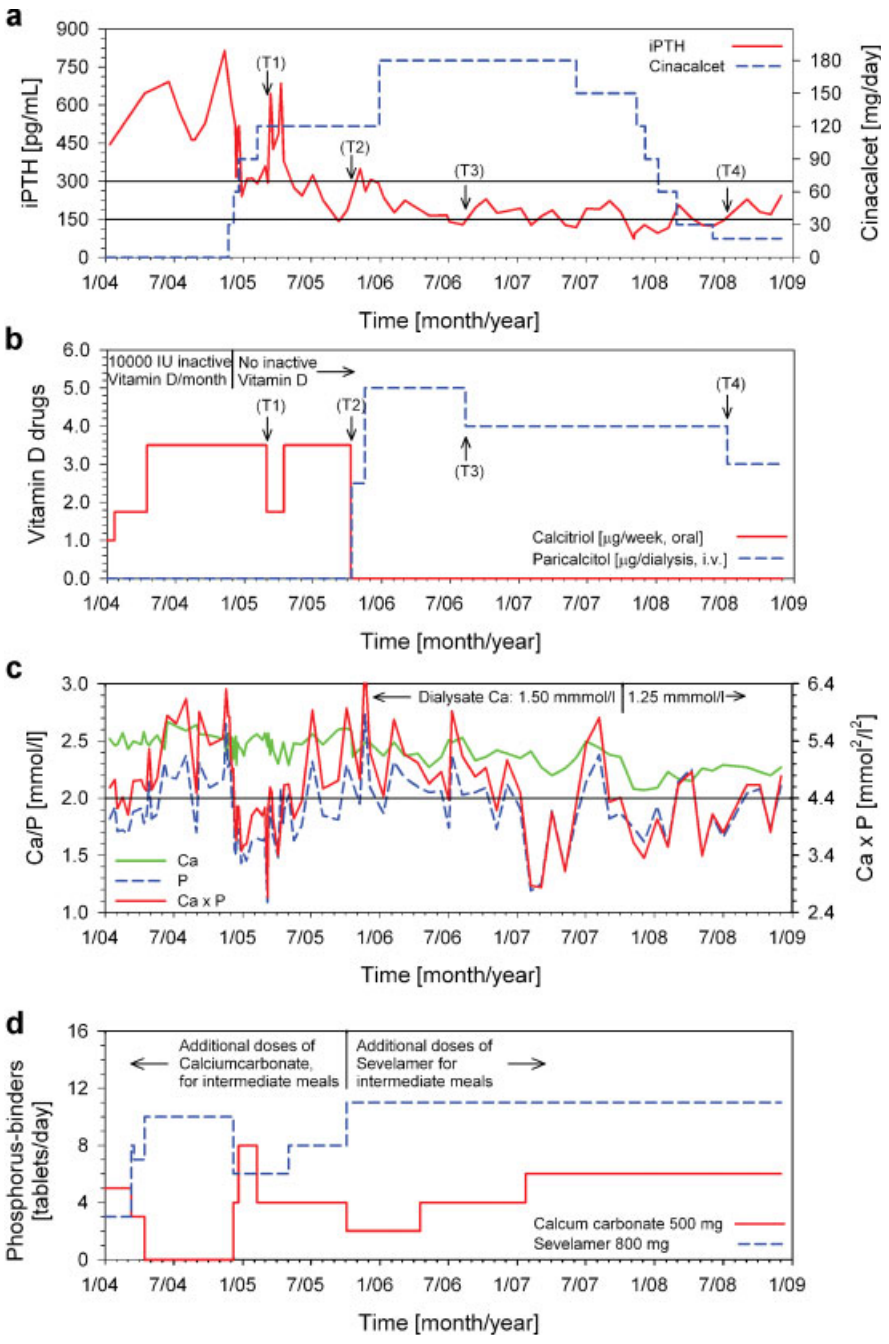

FIGURE 1. *Blood parameters and medicamentations over the reported period. The iPTH target range and the Ca × P threshold recommended[3] are indicated by horizontal lines. Note: iPTH values were converted from pmol/L to pg/mL using a conversion factor of 0.11.[3]*

iPTH in dependence of vitamin D dose suggests a strong influence of active vitamin D on iPTH in combination with cinacalcet. This influence was also seen later (T_2–T_4 in *Figure 1A,B*) after replacing calcitriol with paricalcitol.

In response to several iPTH values below 150 pg/mL, the cinacalcet dose was reduced within 12 months in steps of 30 mg down to an every other day dose of 30 mg (i.e., 4 × 30 mg/wk, *Figure 1A*). While reducing cinacalcet, the paricalcitol dose was kept constant at 3 × 4 µg/week. Later, the paricalcitol dose was reduced to 3 × 3 µg/week (*Figure 1B*). With these cinacalcet and vitamin D doses, iPTH remained in the recommended range within the reported period.

Discussion

Currently, the optimal combination of cinacalcet and vitamin D for the treatment of SHPT in dialysis patients has not been established. In the reported patient, the combination of cinacalcet plus active vitamin D was effective in restoring and maintaining long-term control over iPTH. As cinacalcet acts as a modulator of the Ca-sensitizing receptor, the primary mechanism of the iPTH-inhibition should be expected to be independent from that of active vitamin D. Nevertheless, a complementary effect of cinacalcet and vitamin D on iPTH was observed. As iPTH could be controlled, neither with calcitriol alone nor with cinacalcet and a reduced calcitriol dose, a synergistic mechanism might be hypothesized.

Such a synergistic mechanism might originate from the fact that cinacalcet and vitamin D act at different points of the same iPTH expression pathway.[1] As vitamin D decreases the iPTH mRNA transcription rate and cinacalcet reduces mRNA stability, the expression rate of iPTH may expected to depend on the product of the iPTH mRNA transcription rate and the half life of iPTH mRNA. Hence, the combined effect of cinacalcet and vitamin D on iPTH might be over-additive, that is, synergistic. This interpretation is also supported by a previous observation in the same patient, where an iPTH level larger than 300 pg/mL was treated with calcitriol and where it took 2 months until iPTH decreased. In contrast, the iPTH reduction occurred within 1 week of the combined treatment with cinacalcet when vitamin D was increased. The underlying mechanism for this accelerated response time might be a reprogramming of the parathyroid cells.

After reducing vitamin D (T_1, *Figure 1B*), Ca remained stable (*Figure 1C*) indicating that the observed iPTH increase is Ca-independent. Between 1/2006 and 10/2007, the average Ca decreased continuously (*Figure 1C* and *Table I*). This finding might originate from the replacement of calcitriol by paricalcitol as well as from the general

Table I. Serum values of Ca, P, and Ca × P (mean ± 1 SD) and the fraction for which the Ca × P exceeds the recommended threshold of 4.4 $mmol^2/L^2$ (55 mg^2/dL^2)[3].

Period	Ca (mmol/L)	P (mmol/L)	Ca × P ($mmol^2/L^2$)	Ca × P >4.4 $mmol^2/L^2$
01/2004–12/2004	2.50±0.09	1.95±0.29	4.87±0.76	25/34 (74%)
01/2005–12/2005	2.48±0.09	1.81±0.33	4.47±0.87	12/24 (50%)
01/2006–12/2006	2.41±0.08	2.06±0.19	4.95±0.50	11/13 (85%)
01/2007–10/2007*	2.35±0.09	1.77±0.38	4.16±0.99	4/10 (40%)
10/2007*–12/2008	2.20±0.08	1.86±0.24	4.09±0.56	5/13 (38%)

** Until/from change of Ca in dialysate.*

influence of cinacalcet on Ca/P metabolism. Further reduction of Ca was achieved by lowering the dialysate Ca to 1.25 mmol/L. A moderate increase of calcium carbonate dose did not significantly influence serum Ca (*Figure 1D*). This Ca reduction might have a positive impact on vascular calcification and associated mortality.

As of mid-2007, the cinacalcet dose could be drastically reduced while still controlling iPTH. In the current situation, it might be possible to completely omit cinacalcet. However, calcimimetic compounds improve the decreased sensitivity of the Ca-sensing receptor to extracellular Ca and suppress iPTH over-secretion as well as parathyroid cell proliferation. As cinacalcet probably does not reduce the number of iPTH-emitting cells, it appears likely that iPTH would be only temporally controlled. Therefore, small maintenance doses of cinacalcet are likely to be required.

Whether biochemical control of iPTH leads to decreased mortality in dialysis patients is an open question,[12] which may be governed by the ability of cinacalcet to improve Ca × P. For the reported patient, Ca × P improved over time (*Table I*). This improvement was partly due to the reduced serum Ca, but also due to better phosphorus values (*Figure 1C*). Whether the reduced phosphorus values are related to treatment with cinacalcet is unclear as these are strongly influenced by nutritional intake. At least, serum Ca could be significantly reduced without any influence on iPTH control.

Being aware that a reduced mortality remains to be shown, we draw the following conclusions from the reported case: (1) Cinacalcet plus active vitamin D appears to be more effective than each of the 2 drugs alone. This suggests a synergistic effect, which might originate from the fact that cinacalcet and vitamin D act at different points of the same iPTH-expression pathway.[1] (2) Initial high cinacalcet doses may be significantly reduced after some time, which may be important for cost containment.[13] (3) Serum Ca may be significantly lowered without increasing iPTH and Ca × P can be improved.

Disclosure

Vedat Schwenger, MD participated in the EVOLVE (Evaluation of Cinacalcet HCL Therapy to Lower Cardiovascular Events) study sponsored by Amgen. D&T

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